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Original Articles

SOME COMMENTS UPON ANTIGENS AND THE PRACTICE OF ALLERGY

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CHEMICALLY modified proteins were first thoroughly studied by Obermayer and Pick. They also tested the effect of various physical agents which might modify the structure of the protein molecule. The action of heat, toluol, chloroform, simple acids and alkalies, while modifying antigenic properties, did not alter specificity. When the proteins were diazotized with nitrous acids or iodized with Lugol's solution, their specificity was altered and in this way species specificity could be destroyed. The changes produced were assumed to be due to some substitution in the aromatic radicles of the proteins which appeared to be of supreme importance to antigenic function.

Landsteiner and his collaborators have investigated the subject of compound or conjugated antigens. Landsteiner, like Wells, believes that antigenic specificity depends upon the chemical structure of a small part (the nucleus of the large protein molecule). Pauli, many years ago, showed that the diazo bodies introduced by Landsteiner into the protein molecule entered only the tyrosin and histidin groups.

It has been known for many years that animal proteins such as blood serum may contain several antigenic entities. Dale and Hartley demonstrated the presence of such antigenic entities for englobulin, pseudoglobulin and albumin in horse serum.

Dochez and Avery found in the blood and urine of persons suffering from pneumonia a substance which reacted specifically with pneumococcus immune serum but which was nonantigenic and is now described as a soluble specific substance. Zinsser reported a similar substance for tubercle bacilli which he called "residue antigen."

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It has been repeatedly emphasized that there is a definite relationship between chemical structure and antigenic function, and our present knowledge is a result largely of the contributions of Wells, Obermayer, Pick, and Landsteiner.

Avery and his coworkers have demonstrated a number of interesting facts regarding the rôle of specific carbohydrates in pneumococcus infection and immunity. The specificity for each type of pneumococcus has been found in each instance to belong to the class of sugar-like substances, namely, the carbohydrates. The capsular polysaccharide derived from each specific type of organism is chemically distinct and differentiated sharply from other types of pneumococci. The fact that the particular constituent determining type specificity is chemically a carbohydrate is to be emphasized in that hitherto immunity reactions have been considered exclusively the function of proteins.

Those specific carbohydrates are probably not directly toxic, but indirectly they seem to have a harmful effect—they tend to interfere we know by mobilizing any antitoxins available, and as well exhibit an inhibiting effect on phagocytosis. They probably fall in the category of haptens, i.e., they are incapable of inducing immunity but will give in vivo and in vitro reactions with immune sera.

More interesting to the members of this society is the assertion that these carbohydrates have been found to incite specific reactions in the tissues of sensitized animals and in the skin of patients convalescent from pneumococcus pneumonia.

The capsular carbohydrate of type III pneumococcus was synthesized by Dr. Goebel and coupled with a foreign protein—globulin from horse serum. Animals injected with this conjugated antigen developed in their serum pneumococcus type III specific antibodies.

Studies with other synthesized proteins have shown that if two distinct carbohydrate derivatives are joined separately to the same protein, the resulting immunity following experimental injection is specific for each conjugated antigen. On the other hand if one carbohydrate derivative is joined to two different proteins, the two antigens have an identical specificity. In many respects the carbohydrate fraction seems to determine the type of specificity induced.

Substances similar in character to the haptens of the pneumococci—an important group of substances so labeled by Landsteiner—have been found in yeast cells by Mueller and in tubercle bacilli by Dudley and Laidlaw. Enzymes have been found which have a specific decomposing action on individual haptens.

So far there seems to have been no proof afforded that glucosides by themselves can act as true antigens. The communications made years ago by Ford and Abel have recently been critically reviewed by Branham. There is, however, ample evidence that they can act as haptens,

i.e., give in vitro reactions with immune serum and skin tests on suitably sensitized individuals.

It also has not infrequently been claimed that lipoids may act as antigens. Here also, as with the glucosides, it would seem that while they may act as haptens they are true antigens only when combined with proteins.

Concluding then from the results obtained upon experimental animals, it would seem that at the present time substances which possess antigenic activity must exist in colloidal solution, they must be foreign to the animal producing the antibody, and further they must penetrate beyond those surfaces of the body which protect against foreign colloids.

Yet we have at the present moment no satisfying theories as to the character of the factors which induce on the one hand immunity, and on the other hand sensitization as judged by anaphylactic shock and passive transfer. In tuberculosis both immunity and sensitization can be induced but not passive transfer and in convalescent pneumonia a definite immunity with skin sensitivity to a specific carbohydrate.

I have ventured to present this most incomplete and fragmentary series of comments on antigens as I believe a knowledge of this subject should be the basis for any one who attempts to practice clinical allergy as a lead or as a specialty.

As a specialty it is certainly criticized, and it is certainly widely different from the older and more generally accepted specialties. Those were undoubtedly largely concerned with manipulative experience and more frequently with endoscopic examination of one kind or another. As now practiced, instruments of exquisite design are used, and manipulative experience and precision are or should be indispensable.

There are other considerations which form just as true a basis for specialization. Among these I would place clinical experience, provided it is supported by a knowledge of the essential scientific fundamentals, on a plane that is as satisfactory as any. Granted these two (experience and scientific fundamentals) any one of average ability would be forced to see the limitations as well as the advantages of any method whether of diagnostic or of therapeutic intent; and would be bound to strive for fuller explanations in those instances in which the application of the accepted theories failed to give satisfactory clinical results.

As it appears to me, the practice of allergy at the present time is chiefly menaced in two respects.

The first is the reporting of allergic manifestations in the individual or a disease group when actually or probably they do not exist. The second is the overlooking of some other condition of more importance to the welfare and health of the patient than any symptoms referable to the detected atopen.

In contrast to this is the undoubted benefit and satisfaction (mutual to patient and physician) of suspecting and subsequently proving an allergic basis which has been hidden by unusual symptoms—or missed in the usual history. Such result I believe can only be achieved by those who have paid special attention to and have had a large clinical experience in the treatment of allergic conditions.

In routine clinical work the scratch and intracutaneous test forms actually the basis of allergy. With good instruction it can be easily mastered by any one of average ability. Its interpretation is based upon the history and the complete examination of the patient, and herein lies the value of the physician making a lead or a specialty of allergy not only to the laity but to the profession.

I believe another duty lies upon all of us who accentuate allergy in practice, and it is to acknowledge wherein our accepted methods fail. The result must be twofold; an increase in the care with which we take our histories and make our physical examination, and an attempt within our means of experimental studies. Chiefly through this latter may we hope to put the practice upon more satisfactory foundation.

It has been said of the specialist that he is one who knows a great deal about a very little, and he goes on knowing more and more about less and less until he knows everything about nothing.

I believe this Society brings forth so much and stimulates so much that no persisting member—he must attend every three years to persist—will ever become a specialist according to this definition.

I am indebted to an unpublished manuscript by Dr. J. G. FitzGerald of the University of Toronto for a considerable number of the earlier references.

Zinsser's Textbook, Resistance to Infectious Diseases, ed. 4, The Macmillan Co., gives practically all of the remainder.

THE PREPARATION AND STABILITY OF FOOD ALLERGEN EXTRACTS*†

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PREVIOUSLY[1] we studied different methods of protein extraction for the preparation of allergenic food extracts and found that the clinical activity of extracts made with dilute salt solutions was quite satisfactory and that there was probably no special virtue in the particular saline mixture proposed by Coca.[2] However, for practical purposes it is no less important to know the degree of stability of the active agents in the extracts than to know that they originally contained the active agents. The present study has been made of the stability of certain of the more important food extracts in an effort to prepare one that will retain for relatively long periods the original allergenic activity and sterility, and remain free from visible precipitation of the dissolved materials.

This study has been confined to the preparation of extracts of wheat, eggs, and milk, but the method can be used with other food materials with minor modifications for the individual materials extracted. During our preliminary studies it was noted that wheat extracts are particularly liable to change with time, especially those containing phenol or tricresol which often become black as ink and show considerable precipitation of solids. For this reason a preliminary special study of wheat extracts was made with regard to their stability.

Whole wheat flour was extracted with different strengths of aqueous sodium chloride and sodium bicarbonate solutions to determine if the latter salt possessed any unique advantage. The results are summarized in Table I.

The results indicate no special advantage of the sodium bicarbonate as an extractive agent for protein present so that preliminary study of factors affecting stability of extracts was made with sodium chloride extracts. A 20 per cent extract of whole wheat flour was made with a 5 per cent aqueous solution of sodium chloride and divided into two parts. The firse was treated with tricresol to give a concentration of 0.5 per cent of this preservative, while the second was made slightly

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alkaline and then treated with tricresol in the same amount. The original extract had a P_H of 6.8, and the alkalinized extract had a P_H of 7.5. They were both filtered sterile and then allowed to stand for one month at room temperature. At that time both solutions were black in color and contained heavy, flocculent precipitates but were sterile. Since wheat extracts made with a layer of toluene as a preservative do not become markedly colored on standing, although precipitation does occur, it was apparent that there must be a phenol oxidase present and that the oxidizing reaction might be dependent upon the hydrogen ion concentration of the solution.

TABLE I

N CONTENT OF 5 PER CENT EXTRACTS OF WHOLE WHEAT FLOUR (2.8 PER CENT N CONTENT)

SOLVENT	MG. N PER C.C.	SOLVENT	MG. N PER C.C.
Water	0.19	Water	0.19
1% NaCl	0.31	1% $NaHCO_3$	0.33
3% NaCl	0.33	3% $NaHCO_3$	0.33
5% NaCl	0.33	5% $NaHCO_3$	0.30
10% NaCl	0.29	10% $NaHCO_3$	0.26

More complete series of wheat extracts were then prepared, using a somewhat more dilute extract and varying the hydrogen ion concentration and the preservative added. Ten per cent wheat extracts were prepared with 0.3 M sodium chloride, 0.2 M potassium dihydrogen phosphate, and 0.2 M disodium hydrogen phosphate solutions for extraction; then each of these extracts was divided into three portions, and these were diluted with equal volumes of aqueous 1 per cent phenol, 40 per cent ethanol, and glycerol. The resultant solutions were filtered sterile and allowed to stand six months at room temperature. The neutral or sodium chloride extracts had a P_H of 6.9 to 7.0, the acid or potassium dihydrogen phosphate extracts had a P_H of 5.3 to 5.4, and the alkaline or disodium hydrogen phosphate extracts had a P_H of 7.6 to 7.7. The results are summarized in Table II.

TABLE II

APPEARANCE OF 5 PER CENT EXTRACTS OF WHOLE WHEAT FLOUR AFTER SIX MONTHS

CONTAINS	0.15 M NACL	0.1 M KH_2PO_4	0.1 M NA_2HPO_4
0.5% phenol	Black, turbid	Black, turbid	Brown-black, slight ppt.
20% ethanol	Very pale yellow, slight ppt.	Very pale yellow, slight ppt.	Pale yellow, clear
50% glycerol	Pale yellow, clear	Yellow, clear	Yellow, clear

From Table II it is seen that (1) the presence of phenol leads to the formation of considerable color material with such extracts, and

(2) the presence of 20 per cent ethanol or 50 per cent glycerol stabilizes the solution against precipitation of solids, particularly at an alkaline reaction. The 50 per cent glycerol is preferable to 20 per cent ethanol in this respect.

Since the production of color and precipitation with aqueous phenol extracts might be quite specific for wheat extracts, similar comparisons were made with egg extracts. Egg white was diluted with the same buffer solutions as just described, and the solution made up to contain 0.5 per cent phenol and a content of 0.32 mg. N per c.c. A similar series of solutions were also prepared of ether extracted egg yolk. These solutions were filtered sterile and set aside for six months at room temperature. At that time the alkaline solutions of both the white and the yolk had developed appreciable color, and several had a considerable turbidity although sterile. Alkalinity was of aid in keeping the solutions clear.

The foregoing experiments indicate that a stable extract of both wheat and eggs should not contain a phenol and should have a slight alkaline reaction for best stability. Twenty per cent ethanol or better 50 per cent glycerol were shown to be of aid in stabilizing the solutions against precipitation on standing. Since 40 per cent to 50 per cent glycerol solutions have been shown to be actively bactericidal by Rosenau[3] while a 20 per cent ethanol solution is not, it would seem that the glycerol extract would be the most preferable of the various types considered.

For further study of the stability of food allergen extracts it was decided to adopt a standard glycerol buffer solution for use in preparing extracts that could serve as a future point of reference. The solution adopted is prepared by mixing

1 volume 0.30 M potassium dihydrogen phosphate
(40.85 grams KH_2PO_4 per liter)
4 volumes 0.30 M dipotassium hydrogen phosphate
(52.275 grams K_2HPO_4 per liter)
5 volumes c.p. glycerol

Although the adoption of this particular glycerol buffer solution is largely arbitrary, it presents certain advantages other than fulfilling necessary requirements discovered during the previously described experimentation. The solution is strongly and stably buffered at a slight alkaline reaction, P_H 7.4 and is isotonic and isohydrionic with serum and tissue fluids. It is easily and precisely made and gives extracts that are quite readily filtered through germ-proof filters to brilliantly clear solutions. Due to the bactericidal action of the glycerin, there is no difficulty from bacterial contamination, and the solutions are not sufficiently viscous to cause any difficulties in handling.

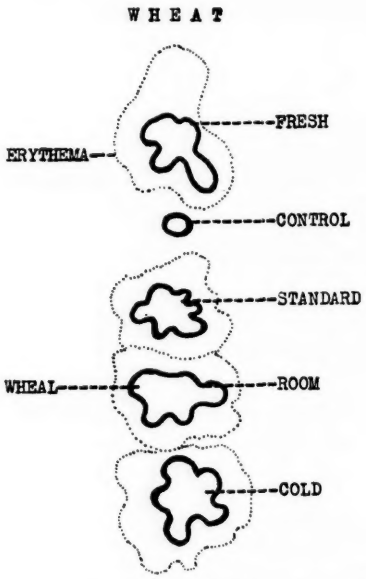

Fig. 1.—Transfer tracings from comparative intradermal tests.
Fresh—Solution made up from wheat at time of testing.
Control—Diluting fluid, 15 per cent alcohol in buffered salt.
Standard—Solution made from precipitated antigen and used for routine testing.
Room—Solution kept at room temperature for seven and one-half years.
Cold—Solution kept in ice box for seven and one-half years.

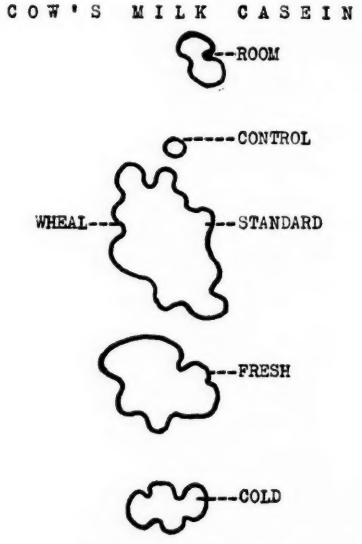

Fig. 2.—Transfer tracings from comparative intradermal tests.
Room—Solution kept at room temperature for seven and one-half years.
Control—Diluting fluid, 15 per cent alcohol in buffered salt.
Standard—Solution made from precipitated antigen and used for routine testing.
Fresh—Solution made up from cow's milk casein at time of testing.
Cold—Solution kept in ice box for seven and one-half years.

Extracts of three of the most common foods, wheat, eggs, and milk, were prepared, using this standard glycerol buffer solution and kept for a long period of time (seven years), and then tested in comparison with freshly prepared extracts made by following the same procedure. The extracts were prepared as follows:

Wheat.—Fifty gm. of air dry, freshly ground wheat flour was extracted with 500 c.c. of standard glycerol extracting fluid for two hours with shaking. After settling for twenty-four hours, the extract was filtered sterile. The total N content was then determined, and

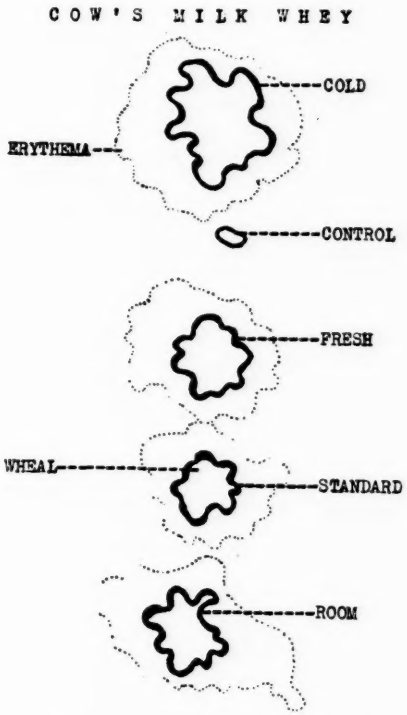

Fig. 3.—Transfer tracings from comparative intradermal tests.
Cold—Solution kept in ice box for seven and one-half years.
Control—Diluting fluid, 15 per cent alcohol in buffered salt.
Fresh—Solution made up from cow's milk whey at time of testing.
Standard—Solution made from precipitated antigen and used for routine testing.
Room—Solution kept at room temperature for seven and one-half years.

the solution diluted with sterile glycerol extracting fluid to a total N content of 0.32 mg. N per c.c.

Egg White.—Twenty-five c.c. of egg white from fresh hens' eggs was mixed with 225 c.c. of 0.3 M standard phosphate buffer solution and 250 c.c. glycerol, then filtered sterile. The total N content was then determined and the solution diluted with sterile glycerol extracting fluid to a total N content of 0.32 mg. N per c.c.

Egg Yolk.—Two yolks of fresh hens' eggs were washed free from adhering white and extracted with 4 portions of ether. Two hundred and fifty c.c. of 0.3 M standard phosphate buffer solution was added, and the solution shaken until the yolk passed into solution. A small ether layer was separated off, and an equal volume of glycerol added. The resultant solution was filtered sterile, the N content determined, and then diluted with sterile glycerol extracting fluid to a total N content of 0.32 mg. N. per c.c.

Milk Casein.—Two and one-half gm. purified casein was extracted with 500 c.c. standard glycerol extracting fluid for two hours with

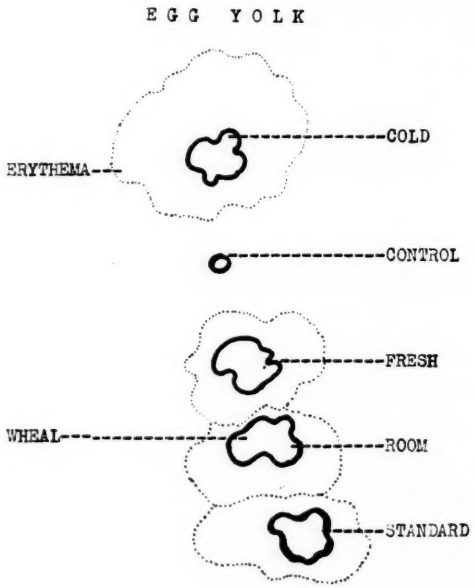

Fig. 4.—Transfer tracings from comparative intradermal tests.
Cold—Solution kept in ice box for seven and one-half years.
Control—Diluting fluid, 15 per cent alcohol in buffered salt.
Fresh—Solution made up from egg yolk at time of testing.
Room—Solution kept at room temperature for seven and one-half years.
Standard—Solution made from precipitated antigen and used for routine testing.

shaking, and after settling for twenty-four hours was filtered sterile. The N content was determined and the solution diluted to a total N content of 0.32 mg. N per c.c.

Milk Whey Protein.—One thousand c.c. skim milk was treated with 50 c.c. 10 per cent acetic acid solution with stirring and after standing an hour the casein was filtered off. The filtrate was then dialyzed in collodion against running water for twenty-four hours. The resulting solution was concentrated by freezing out some ice, and to this solution was added enough solid K_2HPO_4 to make a 0.24 M solution, and enough solid KH_2PO_4 to make a 0.06 M solution. An equal

volume of glycerol was then added, and the extract filtered sterile. The total N content was determined and the solution diluted with standard glycerol extracting fluid to a total N content of 0.32 mg. N per c.c.

In January, 1926, these extracts were prepared and a half portion of each was stored in brown bottles at room temperatures and exposed to diffuse daylight during the day. The other half portion was stored in a cold room, kept at about 40° F., and was exposed to occasional diffuse lamplight. These stored extracts were suitably diluted and tested in comparison with freshly made extracts during April, 1933, an elapsed time of over seven years.

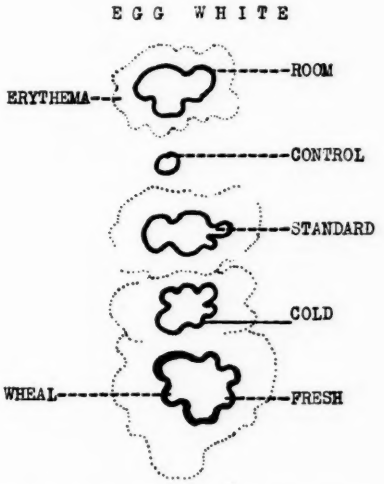

Fig. 5.—Transfer tracings from comparative intradermal tests.
Room—Solution kept at room temperature for seven and one-half years.
Control—Diluting fluid, 15 per cent alcohol in buffered salt.
Standard—Solution made from precipitated antigen and used for routine testing.
Cold—Solution kept in ice box for seven and one-half years.
Fresh—Solution made up from egg white at time of testing.

Dilutions of 1:10 were made from these extracts under sterile conditions and intracutaneous tests were performed as comparisons on the same person. A few of these comparative reactions are shown in the tracings of the skin reactions here shown.

From comparing these reactions on from 16 to 20 persons skin-sensitive to each of the several food antigens, it became evident that there was little or no difference in the allergenic activity of extracts prepared as described, during seven years' storage in the cold room. Storage of these extracts at room temperature appeared not to cause any appreciable loss in activity in seven years with extracts of milk or eggs, but in some test cases there was a slight decrease apparent with the wheat extract stored at room temperature in comparison with

a fresh extract. The apparent decrease is but slight, however, and perhaps may be taken only to indicate the general desirability of cold storage for these biologic products, inasmuch as seven years is a period considerably longer than is usual for the storage of such extracts before use.

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THE PRESERVATION OF POLLEN EXTRACTS BY DRYING AND THE PREPARATION OF CONCENTRATED POLLEN SOLUTIONS*†

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ONE of the difficulties encountered in the treatment of seasonal hay fever is the lack of stability of the extracts used. This has been especially true since the perennial method of treatment has gained favor. The change from an old extract to one freshly prepared increases the danger of constitutional reactions. Various methods have been recommended by clinicians to meet the difficulty. Some mix the old and fresh extracts in various proportions, gradually increasing the percentage of the fresh material until the transfer is completely made to the new extract. Others recommend a decrease of 33 per cent to 50 per cent in the dose when making the change to a freshly prepared extract.

The problem of standardization of pollen extracts has been recently reviewed by Cooke and Stull.[1] They found that extracts made on a weight per volume basis showed a variation as great as 75 per cent in their protein content, while those prepared on a total nitrogen basis varied as much as 50 per cent in their protein content. The deterioration of saline extracts of pollen reported in a later work by Cooke, Vander Veer and Barnard[2] was approximately 50 per cent in one year.

Cooke and Stull recommend the standardization of pollen extracts on the basis of protein nitrogen rather than on total nitrogen or weight per volume. They suggest that 0.00001 mg. protein nitrogen (P.N.) be accepted as one pollen unit, since this, in their experience, is practically the smallest dose required for the most sensitive patient. While this method of standardization is the most acceptable one offered, and the only one that has a chemical basis, it involves practical difficulties which will probably prevent its general acceptance by the allergist who has neither special training in biochemistry nor the laboratory facilities for determining the nonprotein and the total nitrogen content—determinations necessary in order to arrive at the value of the protein nitrogen of each freshly prepared pollen extract.

Experience in our laboratory indicates that proteins dissolved in water or saline may be dried at 40° C. with no loss of antigenicity.

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The activity in the dried state remains unaltered indefinitely. Coca, Walzer and Thommen[3] report that on extraction, a forty-year-old specimen of *Ambrosia trifida* showed practically the same activity as a fresh specimen.

The following report deals with the effect of drying on the solubility and activity of ragweed pollen extract.

PROCEDURE

Six grams of giant and 6 grams of short ragweed pollen were completely defatted in a Soxhlet with c.p. anhydrous ethyl ether. The 12 grams of pollen were extracted in a mechanical shaker for twenty-four hours with 400 c.c. distilled water. The supernatant fluid was then filtered off and divided into four equal portions. One of these specimens was passed through a Seitz filter after the addition of phenol to a 0.1 per cent concentration. The nitrogen content of this extract determined by micro Kjeldahl was 0.4 mg. per c.c. The other three specimens, each 100 c.c. in volume, were dried in separate containers in a drier designed for such use by Dr. William H. Welker, Head of the Physiological Chemistry Department of the University of Illinois College of Medicine. This is a specially designed apparatus which delivers filtered air warmed to 40° C. over the material to be dried. A liter of solution placed in one of the compartments can be dried in about twenty-four hours under ordinary weather conditions.

THE SOLUBILITY OF THE DRIED POLLEN EXTRACT

Two of the dried specimens were used to determine the solubility of the material. Each of these was allowed to swell for several hours by moistening with a few drops of water. After the addition of 10 c.c. distilled water to one of the two specimens, the solution was dark brown with a fine flocculent suspension. The material was centrifuged thoroughly at this point and a few cubic centimeters of the supernatant fluid were carefully removed with a pipette. This was filtered, covered by toluol and allowed to stand in the refrigerator for two days. No precipitate appeared at the end of that time. The nitrogen content determined by the micro Kjeldahl method was 1.81 mg. per c.c. This, it may be assumed, is the nitrogen content of a saturated pollen extract made from the particular batch of ragweed pollen used.

By adding water gradually to the two specimens selected for solubility determinations, it was found that the minimum amount of fluid necessary to redissolve all of the water soluble material was 22.5 c.c. A very small amount of fine granular residue, just barely sufficient to cover the bottom of a 15 c.c. centrifuge tube, remained insoluble on repeated shaking with distilled water. The nitrogen content of the redissolved aqueous solution was 1.8 mg. per c.c. or a total nitrogen of 40.5 mg. for the 22.5 c.c. The small residue which was insoluble in

water dissolved readily in 5 c.c. of 0.2 per cent sodium carbonate. Its nitrogen content was 0.036 mg. per c.c. or a total of 0.18 mg. for the 5 c.c. Thus the entire dried specimen redissolved in water and sodium carbonate contained 40.68 mg. of nitrogen. It will be recalled that before drying, the original volume was 100 c.c. with a nitrogen content of 0.4 mg. per c.c. or a total content of 40 mg. of nitrogen. The discrepancy of 0.68 mg. of nitrogen in the determinations before and after drying is well within the limits of error in the micro Kjeldahl method.

It may be concluded from these figures that practically all of the pollen extract could be redissolved in distilled water after drying at 40° C. The residue which was soluble in sodium carbonate but insoluble in water gave positive cutaneous reactions in known hay fever patients.

THE ACTIVITY OF THE DRIED AND REDISSOLVED POLLEN EXTRACT

The next question to be answered was whether the antigenicity of the pollen had been altered by drying at 40° C. By redissolving the dried material in less than one-fourth of the original volume of water, a highly concentrated pollen solution had been prepared which in its nitrogen content (1.8 mg. per c.c.) was four and a half times as concentrated as the original undried extract (0.4 mg. N per c.c.). In terms of weight per volume the concentrated extract would be considered an 18 per cent pollen extract. Similar concentrated pollen extracts were reported by Brown.[4] He, however, decided that a 12.5 per cent pollen extract was the most potent solution that could be prepared.

Twenty known ragweed sensitive patients who had received no prophylactic treatment during that season were selected to determine the relative activity of the dried and redissolved extract as compared with the original undried material. Each of the two extracts were diluted to the following concentrations for intracutaneous tests: 0.0005, 0.0001, and 0.00001 mg. of nitrogen per c.c. The injections were made on the outer surface of the upper arm. Using a tuberculin syringe, great care was taken to inject, as nearly as possible, only 0.02 c.c. for each wheal. After ten patients had been tested in this manner, it was decided that the intracutaneous method, while much more delicate than the cutaneous, did not lend itself to a close comparison between the reactions of solutions that were not widely divergent in their concentrations. Dilutions as close as 0.0005 and 0.0001 of nitrogen per c.c. made from the same extract failed to show even a two-to-one proportional difference in the size of the wheals produced when read after five, ten and twenty minutes. It is possible that if we were able to measure the effect of the intracutaneous injection on the deeper tissues as well as upon the epidermis itself, this method would be satisfactory for a comparison of the relative potency of antigenic proteins.

The cutaneous method proved to be more satisfactory for the comparison of the relative activity of the two pollen extracts. With a multiple scarifier[5] whose blades can be adjusted to produce scarifications of uniform depth and length, wheals were obtained of almost duplicate size with the same pollen concentrations. And when different pollen concentrations were used the variations in the size of the wheals were much closer to the proportion of nitrogen concentration by this method than by the intracutaneous technic.

The concentrated pollen extract (referred to hereafter as extract C) and the original undried solution (designated as extract D) were each diluted to 0.1, 0.01, and 0.001 mg. of nitrogen per c.c. Six scarifications were made with the multiple scarifier along the inner and six along the outer margins of the forearm. Dilutions of the same concentration were placed over the scarifications made by the same knife, extract C along the inner margin and extract D along the outer margin of the forearm. In addition to the three dilutions of the two extracts, a fourth test was used as a control for the correct adjustment of the instrument blades. This consisted of a drop of extract D having a concentration of 0.01 mg. of nitrogen per c.c. placed over the fourth scratch on each side of the forearm. The uniform adjustment of the blades was indicated by the similarity in the size of the reaction at this last site. At the end of fifteen minutes, the reactions were outlined in ink and transferred to blotting paper for comparison. The size of the skin reactions produced by the two extracts were almost uniformly alike for the same nitrogen concentration in all twenty patients.

Ten of these patients were then treated with extract C after this had been diluted to the concentrations suitable for treatment, and ten with extract D. Four of the twenty were highly sensitive individuals who were intolerant to any but the most gradual increase in doses. After each of the patients had received from ten to eighteen pollen injections of increasing concentrations, an interchange in extracts was tried in each group, giving those who had received extract C, extract D, and vice versa. The dose in each case was increased by the usual amount except where such procedure was contraindicated by the severity of the previous reaction. In such cases the previous dose was repeated. No constitutional reaction occurred in either group of patients. This, together with the results of the skin tests, indicates that the concentrated extract made by drying and redissolving in a smaller quantity of water than the original solution, is actually proportional in its potency to its nitrogen concentration (1.8 mg. per c.c. or an 18 per cent pollen solution). It also indicates that the potency of the extract was not diminished by drying at 40° C.

THE ACTIVITY OF DRIED POLLEN EXTRACT AFTER EIGHTEEN MONTHS

After being kept in a dried state for eighteen months one of the specimens was redissolved. It was diluted to 0.1, 0.01 and 0.001 mg. nitrogen per c.c. concentrations. These dilutions were compared by the cutaneous test, as previously described, with the same concentrations of a freshly prepared pollen extract made from the same batch of ragweed pollens. There was no loss in the activity of the material as determined by the skin tests. An interchange of the extracts made on two groups of five patients each, as outlined previously, also failed to show any diminution of the potency of the dried extract.

DISCUSSION

The method of preparation and preservation of pollen extracts described offers several practical advantages to the allergist. First, after the preparation of the primary extract, the material when dried at 40° C. either in vacuo or under a warm air current is stable and offers a readily available source of material for the quick preparation of an unaltered pollen solution. Experience with other proteins indicates that the antigenicity of the material in a dry form is retained unaltered for a practically indefinite period.

The ease of preparation of fresh material from the dried extract is likewise an advantage, especially when the weight per volume or the nitrogen content of a definite amount of pollen extract to be dried, is known. Either all the material or a definite portion of it (by weight) may be redissolved by the use of any one of the solvents preferred by the allergist. The volume of the solvent used will depend upon the desired concentration of the extract. One may thus prepare, within the limits of the solubility of the dried extract, a pollen solution of any desired potency.

The use of distilled water for the original extraction permits the material to be dried with no danger of altering the protein. Numerous workers, among the most recent of whom are Stull and Cooke,[6] have shown that the antigenic material in pollens is completely water soluble. If distilled water is used to redissolve the dried material, any one of the substances used for the preservation of pollen extracts may be added, as sodium chloride, glycerin, glucose, phenol, or sodium carbonate. This should be done before the solution is sterilized by Berkefeld filtration.

The advantage of a pollen solution as concentrated as 1.8 mg. nitrogen per c.c. is in its greater stability. It is the general experience of immunologists that a concentrated protein solution loses its antigenicity less rapidity than a dilute solution. It is also the general experience of allergists that the more dilute pollen solutions which are used early

during a course of treatment deteriorate much more rapidly than the concentrated stock solution. It is my intention to report, at a later date, observations on the relative rate of deterioration of pollen solutions of various concentrations.

CONCLUSIONS

1. Ragweed pollen extract may be dried at 40° C. with very little loss in its solubility and no demonstrable change in its potency.

2. A highly concentrated pollen extract may be prepared by redissolving the dried material in a smaller quantity of water than that used for the original extraction. The most concentrated solution prepared contained 1.8 mg. nitrogen per c.c., the equivalent of an 18 per cent pollen extract.

3. The concentrated extract prepared in this manner had a potency which was proportional to its nitrogen content when compared with the original undried material.

4. The dried material showed no loss of activity when redissolved after eighteen months.

5. The chief advantage of this method of preparation and preservation of pollen extracts is that it provides a readily available supply of pollen stock which is preserved by drying, and which can easily be made into a solution of a definite potency.

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STUDIES IN POLLEN POTENCY*†

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A NUMBER of years ago it occurred to one of us (S. M. F.) that there is a glaring discrepancy between the accepted number of pollen granules which produce hay fever symptoms by natural exposure and the amount of pollen that can be injected or applied topically before such symptoms are produced.

Most of our ragweed-sensitive patients will have unmistakable symptoms with a concentration of 25 pollen granules per cubic yard. If a person inhales 20 cubic yards of air during the twenty-four-hour period, the total number of such pollen granules inhaled will be 500. Presumably not all of these particles will land on the mucous membranes. Furthermore, at any given moment the person is exposed to only a fraction of this number. Yet the instillation at *one dose* of 0.1 c.c. of 1:4,000 ragweed pollen extract—which represents about 10,000 granules—into the nasal cavity or into the conjunctival sac will seldom produce hay fever symptoms.

As a matter of fact, the variation between the two situations is even wider. In the case of natural exposure, symptoms will probably result after an hour's contact with the pollen, which represents in the instance cited only about 20 ragweed pollen granules. By injection and nasal or conjunctival instillation the same patients can tolerate the equivalents of 30,000 or 40,000 pollen granules.

The above considerations are of more than theoretical interest. It is barely possible that the explanation of this discrepancy may throw some light on the differences in mechanism of natural pollen exposure and that of present pollen therapy. This, in turn, might lead to more effective methods of treatment.

With these thoughts in mind the probable explanation of the above observation was considered. Two major possibilities presented themselves which may be formulated in the following queries:

I. Are the accepted methods of estimating the amount of pollen to which one is exposed correct? II. Is the discrepancy due to a difference between activity of the pollen encountered naturally and pollen as utilized in treatment?

Under the first heading several approaches may be offered.

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†Read at the Eleventh Annual Meeting of the Association for the Study of Allergy, at Milwaukee, June 12, 1933.

(Ia) *Is the amount of air inhaled during the twenty-four-hour period approximately correct?* Simple mathematical computations on the basis of 500 c.c. of air per inhalation and 20 inhalations per minute give a result of less than 20 cubic yards of air in twenty-four hours. The figure would, of course, be varied some by exercise, fever, etc.

(Ib) *Is the pollen contact per cubic yard actually represented by the present figures derived by the gravity method of counting?* While physical laws indicate that such mathematical deductions should be correct, some doubt was cast upon them from practical considerations. To answer that question two or three experiments were tried.

1. The bottom of a Gladstone bag having a capacity of $\frac{1}{10}$ of a cubic yard was covered with glass vaseline-coated slides. The bag was opened outdoors and kept open for two or three minutes in order to allow a free interchange of air. It was then closed and placed in a paper bag and thoroughly sealed. This was allowed to stand in a closet overnight in order to allow the pollen to settle on the slides. The latter were removed the following day and placed in slide boxes. The entire surface of all the slides was examined under the microscope at a time when the air was free from pollen. The total number of pollen granules seen multiplied by 10, which *was the actual number of pollen granules per cubic yard at the time of exposure*, did not vary more than 50 per cent from the hourly and twenty-four-hourly gravity counts.

2. Direct figures obtained by O. C. Durham[1] by means of an air pump closely approximated the gravity counts.

3. It may be argued that there is a possibility that the physiology of breathing may modify the number of pollen granules inhaled. O. C. Durham[2] has experimented with a mask with a breathing valve, on the inside of which the pollens are caught on a glass slide. This should give us a measure of the amount of pollen inhaled. At the present time, however, no figures are available.

(Ic) *Is the number of pollen granules that come in contact with the mucosa actually the same as the number in the air?* It may be said that there is ample opportunity for this number to be less, but very little likelihood of its being more.

Having practically exhausted the important considerations under the first major heading, we may now turn to the second: Is the discrepancy due to a difference between activity of the pollen encountered naturally and pollen as utilized in treatment? The first question we tried to answer, was:

(IIa) *Does pollen fresh from the plant differ from stored pollen?* Reference to that possibility occurs here and there. Blackley[3] was quite firmly of the opinion that the fresh pollen is more toxic than the stored.

A giant ragweed plant was brought into the clinic. Pollen was removed directly from the flowers and placed into the conjunctival sac.

The amount of pollen was approximated by previous experimental counts of the numbers contained in a definitely sized particle. While no great accuracy can be claimed for such a procedure, it must also be argued that enormous variations in potency would still be evident.

In 8 ragweed-sensitive patients this fresh whole pollen, taken directly from the flowers, was applied to the conjunctivae and compared with corresponding amounts of whole pollen stored from the 1931 season. Little difference was evident, although whatever difference was present was in favor of fresh pollen.

In 8 patients, 5 of whom were also in the previously mentioned group, fresh pollen suspended in mineral oil was compared with 1931 pollen treated in a similar manner. Very little difference in the conjunctival reactions was shown.

A few limited experiments comparing the intradermal reactions of ragweed pollen extracted two days after collection with that of the extract of stored pollen from the previous season gave no conclusive results.

(IIb) *Does ordinary extraction diminish the potency of pollen?* It is reasonable to suspect that an extract of pollen prepared by any of the well-known methods may not be representative either quantitatively or qualitatively of the potency of the crude pollen. With respect to quantitative differences there is suggestive evidence, since many observers have been able to obtain allergenic extracts after repeated extractions of the pollen. On that basis, Murphy,[4] in 1929, described a method of using pollen suspensions in testing and treatment. While his results were interesting, the clinical interpretation was not definitely decisive to enable us to conclude that the whole pollen was sufficiently more potent as to explain the differences between natural and artificial exposures, to which we have already alluded.

On first thought the best means of solving this problem of potency would be to make intradermal comparisons between the extracts and the whole pollen. However, we must consider that it is not uncommon for ragweed-sensitive persons to give an intradermal reaction with 0.2 c.c. of the one to one hundred million extract or, in some instances, even with one to one hundred billion dilution. This represents $\frac{1}{12}$ or $\frac{1}{12,500}$ part of a pollen granule. The impossibility of measuring such quantities with pollen suspensions is apparent.

We therefore confined our studies in this case to a comparison between whole pollen and pollen extract by conjunctival and nasal instillation. Varying and definite amounts of the giant ragweed pollen collected during the 1931 season were used in the form of the crude pollen, and its extract for comparison. The variations in the number of pollen granules or the equivalent extract instilled into the conjunctival sac were as follows: 400; 4,000; 8,000; 10,000; 20,000; 30,000; 40,000;

60,000; 80,000; 100,000; 200,000; and 400,000. Table I shows the results of such tests. Each figure represents the minimum number of pollen granules (or an equivalent extract) required to produce a positive reaction. It will be noted that in every instance less of the whole pollen was required to give a reaction than the extract.

In nasal testing similar procedures were used. One-tenth cubic centimeter, representing the number of pollen granules as previously outlined, was placed as nearly as possible against the turbinate. A reaction was noted by any or several of the following symptoms: itching, sneezing, nasal obstruction, nasal discharge, and visible swelling of the mucosa or narrowing of the passage. Reactions were much more difficult to judge than in the conjunctival experiments and at times the results were in doubt. There is doubt whether the material always reached the sensitive portions of the mucosa. It is possible that the instillation of the pollen in the form of a spray may have been more effective.

TABLE I

CONJUNCTIVAL INSTILLATION OF POLLEN*
COMPARISON BETWEEN WHOLE POLLEN AND POLLEN EXTRACT
(Giant Ragweed, 1931)

	WHOLE POLLEN	EXTRACT
David R.	200,000	400,000
Mildred V.	40,000	100,000
Robert B. (No. 1)	60,000	200,000
Robert B. (No. 3)	100,000	400,000
Bruno Z.	10,000	100,000
Sylvia Z.	80,000	400,000
		negative
Michael T.	20,000	30,000
Samuel R.	40,000	60,000

*The figures indicate the smallest number of pollen granules which were required to produce a positive reaction.

Table II shows a comparison of the whole giant ragweed pollen of the 1932 season compared with its extract. The number of whole pollen granules required to produce positive reactions apparently showed no marked difference from the extract. It is rather difficult to explain why there is less difference between the reaction of whole pollen and extract nasally and a more decided difference conjunctivally. Further experimentation will be necessary to clear up this point.

(IIc) *Does the nasal mucosa (or bronchial) or its secretion alter the toxicity of pollen?* It is theoretically possible that artificial solvents fail to extract an unknown toxic fraction of the pollen which the tissues or their secretions may be able to remove. In 1924 Armstrong and Harrison[5] attempted to shed some light on this question by testing against antisera a mixture of pollen and nasal secretions obtained from actively suffering hay fever patients. The results were inconclusive. Neverthe-

less, this thought should stimulate more extended experimentation. We have begun such studies, but they have not progressed far enough to justify an expression of opinion.

(IId) *Is it possible that a single application of a comparatively large dose of pollen may fail to produce reaction, while frequently repeated minimal doses (such as occur naturally) may produce symptoms?* Here again there is a fair likelihood of explaining some of the discrepancies described. It is also possible, as mentioned previously, that a more diffuse distribution of the pollen in the nasal mucosa, such as is encountered naturally, may be more effective in producing reaction. Further observations are necessary on this question.

TABLE II

NASAL INSTILLATION OF POLLEN
COMPARISON BETWEEN WHOLE POLLEN AND POLLEN EXTRACT

(Giant Ragweed)

	POLLEN NO. 2 (Collected 8/21/32)		POLLEN NO. 3 (Collected 9/4/32)	
	WHOLE POLLEN	EXTRACT	WHOLE POLLEN	EXTRACT
Mildred V.	30,000	30,000	40,000	40,000
Samuel R.			30,000	200,000
Anna V.			30,000	60,000
Richard R.	20,000	20,000	30,000	30,000
Arthur H.	30,000	40,000	20,000	60,000
Helen H.	30,000	20,000	30,000	20,000
John S.			30,000	20,000

In connection with studies on pollen potency other observations should be recorded. Huber[6] noted that specimens of pollen obtained from various commercial sources varied considerably in their reactivity. Thommen[7] tested the pollen of giant and low ragweed obtained from various parts of the United States and concluded that the hay fever producing substance is a constant feature of such pollen, irrespective of the region in which the plant grows. He does not mention any quantitative studies, however. Lichtenstein[8] tested by the intradermal method ragweed pollen extracts obtained from various commercial houses and other sources and found very little difference in potency.

In connection with our studies on pollen potency other factors which might affect this quality were investigated. We wish to make brief comment on two points: the variation of pollen potency from season to season and the variation during the individual season.

1. *Variation of Pollen Potency in Different Seasons.*—A number of allusions exist in hay fever literature with the opinion that the potency of pollen may vary from year to year. Experimental proof for such assertions is difficult to find. Wilmer and Cobe[9] contend that the potency of pollen is dependent in part on the various climatic changes, and will vary from season to season and in portions of the same season.

Wilmer and Cobe say further[10] that "the inconsistent results of treatment over several years depend on the fact that the active principle of most pollen varies from year to year dependent on varying climatic factors." They thought that plants raised under ideal conditions might produce a less variable and more potent pollen. Comparing the pollen of hothouse grown short ragweeds (1931) with pollen of the same season obtained from several commercial houses, they concluded that the former was more potent. Scratch tests were used for comparison, using extracts of 1:50 and 1:500 and determining the relative size of the reactions. No attempt was made to determine by dilution experiments the lowest concentration giving a positive reaction.

We studied the potency of ragweed pollen collected during various seasons as determined by intradermal tests. Specimens of giant ragweed pollen collected during the seasons of 1926, 1927, 1928, 1930, and 1931 were extracted simultaneously with glycerin-Coca solution. Dilutions were made in multiples of 10 from 1:100 to 1:100,000,000,000. Intradermal injections were made with 0.02 c.c. of the dilutions to be tested. In the higher concentrations no differences were apparent. However, when the more dilute solutions were used, a dilution was eventually reached in which some of the pollens showed a marked diminution or a total absence of the reaction.

The tracings of these reactions are recorded in Fig. 1. It will be seen that for the most part the 1927 and 1928 pollen, and particularly the latter, were less potent than the others. It may be argued that these pollens deteriorated because of age. This is refuted by the fact that the 1926 pollen was considerably stronger. That aging of dry pollen has very little effect on potency is evidenced by the observation of Thommen[7] who tested an extract from the pollen of giant ragweed collected on August 22, 1887, and preserved in a private herbarium. He found that the extract was practically as active as one prepared from pollen collected in 1926.

In Fig. 1, under the 1930 and 1931 seasons, are compared tracings of reactions obtained from the pollen of giant and short ragweed. While there is a slight difference, the variation is not as marked as that in the pollens of the giant ragweed.

We realize, of course, that it is possible that the variation in the potency of the pollen collected during various seasons may be explained by other factors, such as collection during different parts of the season, collection at various localities, different methods of collection, etc. We may say here that these pollens were collected and stored under uniform conditions by a botanist* experienced in this field. We must admit,

*We wish to acknowledge our gratitude to O. C. Durham, chief botanist of Abbott Laboratories, for the cooperation of furnishing these pollens.

however, that these experiments are only suggestive and not conclusive, since they are dependent on results obtained with single specimens of pollen.

2. *Variation of Pollen Potency During Season.*—The question of whether the toxicity of pollen varies with the stage of the season has always been of interest to us in the attempt to correlate such an idea

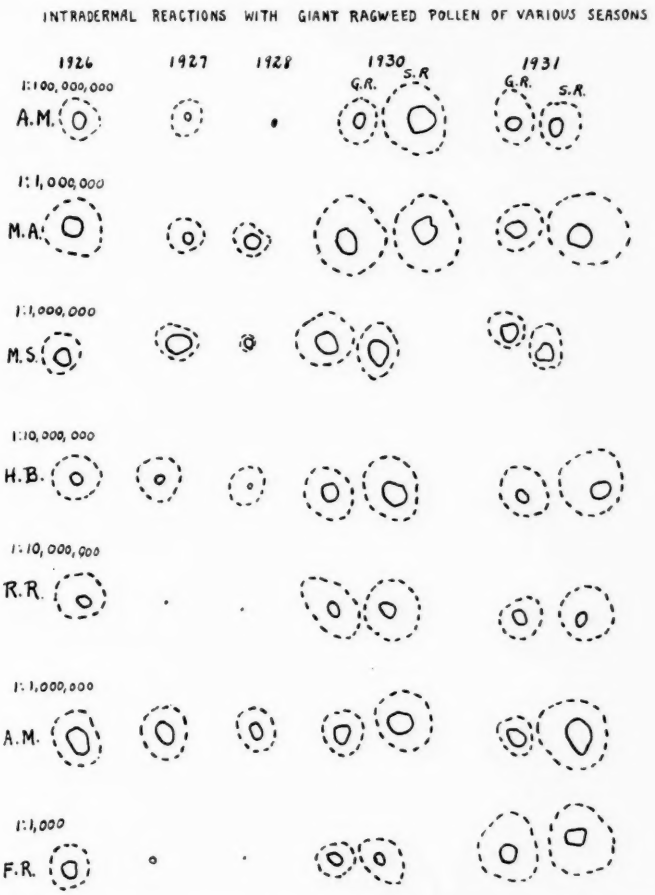

Fig. 1.—Tracings of the wheal and erythema produced by intradermal injections of pollen. Only those reactions which were of high enough dilution to bring out any possible differences in potency are shown here. The year of collection of pollen is recorded at the top of the illlustration. The figures on the side refer to the dilutions of the pollen extracts. S.R.=Short ragweed. G.R.=Giant ragweed.

with the symptoms of the hay fever patient and with the selection of the time for collection of pollen for therapeutic purposes.

Studies were made with three specimens of giant ragweed pollen collected respectively, on August 11, August 21, and September 4, 1932. Nasal and conjunctival instillations were made with the whole pollen suspended in salt solution, and the smallest number giving a reaction

TABLE III

COMPARISON OF POTENCY OF POLLEN (GIANT RAGWEED) COLLECTED AT VARIOUS TIMES OF SEASON

No. 1 Collected Aug. 11, 1932; No. 2 Collected Aug. 21, 1932; No. 3 Collected Sept. 4, 1932.

	NOSE WHOLE POLLEN			EYE WHOLE POLLEN			INTRADERMAL EXTRACTS		
	NO. 1	NO. 2	NO. 3	NO. 1	NO. 2	NO. 3	NO. 1	NO. 2	NO. 3
Robert B.			20,000	60,000	40,000	100,000			
Sylvia Z.	30,000	30,000	40,000	80,000	400,000				
Francis R.		40,000	30,000				1:10,000	1:10,000	1:10,000
Mildred V.		20,000	40,000				1:10 billion	1:100 billion	1:100 billion
Helen H.		30,000	40,000				1:1 million	1:10 million	1:10 million
Bruno Z.	400,000		200,000	10,000	20,000		Neg.		
Richard R.		20,000	30,000				1:100,000	1:100,000	1:1 million
Arthur H.		30,000	20,000				1:100,000	1:100,000	1:100,000
Corrine S.				400,000	80,000				
Marie H.				40,000	40,000				
John S.				60,000	60,000				
Anna M.							1:100 billion	1:10 billion	1:100 million
Helen S.							1:100,000	1:1 million	1:1 million

was recorded. Diluted extracts were tested intradermally as previously described, and the highest dilution giving a reaction was noted.

Table III shows the results of these studies. It will be seen that while differences exist here and there, some in favor of one specimen, some in favor of the other, the net results must be interpreted as a failure to show any marked or constant differences in these pollens.

SUMMARY

1. A discrepancy exists between the number of pollen granules which produce hay fever by natural exposure and the amount of pollen extract that can be injected or applied locally to the nose or eye.

2. This variation cannot be explained by assuming that the usual gravity method of pollen counting is incorrect, since direct determination of the pollen in a measured quantity of air gave figures approximating the latter.

3. Although fresh pollen appears to be slightly more toxic than the stored pollen and although whole pollen is more potent than the extract in many instances, yet the variations are not sufficiently great to explain the clinical observations satisfactorily.

4. It is possible that the natural method of exposure by frequent contact with minimal doses of pollen may be more effective in producing hay fever than an application of a comparatively massive dose at one locus. This requires further investigation.

5. The possibility also exists that the nasal or bronchial mucosae, or their secretions, are capable of extracting a more potent fraction from pollen than is obtained with artificial solvents.

6. Incidental experiments with giant ragweed pollen collected at various stages of the season show very little variation in potency.

7. Comparison of potency of ragweed pollen collected during various seasons shows some distinct variations in potency.

8. The purpose of this paper is not to record a series of complete observations but to indicate some suggestive findings and theories which may stimulate further and more productive work in this field.

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Bruno Z.	400,000		200,000	10,000	20,000		Neg.		
Richard R.		20,000	30,000				1:100,000	1:100,000	1:1 million
Arthur H.		30,000	20,000				1:100,000	1:100,000	1:100,000
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185 N. WABASH AVENUE

INTRADERMAL POLLEN THERAPY DURING THE ATTACK*

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THIS paper presents the information gained from six years' experience with the intradermal method in the treatment of hay fever during the attack.

In 1926 I[1] reported "The Relief of Hay Fever by Intradermal Injections of Pollen Extract" in 29 cases. Thommen,[2] who independently developed a similar technic at about the same time, has continued to use it, and says that he considers it "the method of choice in the administration of all phylactic treatment." Duke[3] who "used the method three years with the best therapeutic results . . . obtained by any method," has abandoned it in favor of subcuticular injections controlled by the use of a tourniquet and the admixture of adrenalin and ephedrin with the pollen extract. His objection to intradermal pollen therapy was that it caused too many scars and too many constitutional reactions.

The work covered by this report was done in central Arizona under conditions peculiar to the Southwest. Fertile soil, a warm dry climate, and abundant irrigation favor a rank vegetation, much of which is wind pollinated. There is little rain, and pollen remains a long time in the air and still longer in the dust. The pollinating season is nine months long, and in protected places some plants bloom sparingly in the three remaining months. This pollen incidence has been more fully described in a recent publication.[4] It constitutes a fairly severe test of any therapeutic method employed against it.

The present report is based on the records of 322 patients who were treated during the attack in 545 hay fever seasons. The seasons of those patients who were treated more than one year are not necessarily consecutive; 31 such patients obtained relief which persisted without further treatment for one to four years, after which their symptoms recurred. The patients were of all ages, from three to seventy-six years; females outnumbered the males approximately two to one. Pollen asthma was common, being frequently the chief complaint. Eczema, or more frequently urticaria, limited to the extremities and demonstrably caused by pollen, was seen occasionally.

Sensitizations were determined in the usual way, by dermal and intradermal testing related to a careful anamnesis. Treatment was carried out only with those pollens or dusts to which the patient was

*Read at the Eleventh Annual Meeting of the Association for the Study of Allergy, Milwaukee, Wis., June 12 and 13, 1933.

markedly sensitive and to which he was exposed at the time when he had hay fever. Bermuda grass, with its prolonged and plentiful pollen production, was the chief offender. Next in importance were careless weed and Russian thistle; then came the *Franserias,* the Arizona ragweed relatives; and finally the trees, cottonwood, ash, and olive. All these had a few cases to their credit as sole sensitizers, but mostly they were associated with Bermuda grass in multiple sensitizations. Orris root also entered the picture, being the chief cause in 5 cases and complicating 60 more.

About one-half of the patients were observed for two or more years, and 18 of these, who at first reacted to one pollen only, became multisensitized in a later year. This new sensitivity could not be detected by the scratch test in its first year; the intradermal test was required to reveal what was interfering with successful treatment.

Food tests were made only when the examination, including the history, aroused the suspicion that a food allergy was complicating the clinical picture; or when pollen treatment alone was unsuccessful. A few such sensitizations were found and corrected; no doubt some others were overlooked. On the whole, however, sensitivity to foods did not play an important part in this series of seasonal hay fevers.

TREATMENT

The technic has been changed but little from that published six years ago. Extracts of naturally ripened local pollens, triturated and made up in Clock's or, more recently, in Stier's solution in the proportion of 1:50, are diluted with Coca's fluid, or with 0.4 per cent phenol in distilled water, to the 1:500 and 1:5000 strengths. The offending pollens having been identified and the degree of sensitivity roughly determined by skin testing, the first dose is the intradermal test, which is never more than 0.02 c.c. of the 1:5000 solution. The patient waits for at least twenty minutes so that the reaction may be observed, and this is done after every injection. The patient returns next day and reports the size of the local reaction, how long it lasted, and its effect on the symptoms. The dose is increased daily as tolerance permits until the local reaction at its height, some three or four hours after the injection, is about the size of the patient's palm; some swelling should remain for twenty-four hours. With some patients the dose can be doubled each time; others tolerate only a fourth or a half of that increase, and some, especially when the pollen curve is rising, stand no increase at all. If the local reaction is still hot and swollen, no dose is given until it has nearly subsided, which it always does by the second day. The dose has to be estimated carefully for each patient at every treatment. Upon this individualization and upon the

technic of injection depend the success and the safety of the therapy. The permissible margin of error is small.

It is necessary that the pollen extract be placed strictly within the skin, and as superficially as possible. The point of a fine sharp needle, 27 gauge, is engaged in the epidermis; the bevel is turned outward, the syringe lowered nearly flat against the skin and the needle advanced until its bevel is just hidden. Then the dose is slowly injected; it should appear immediately as a superficial wheal with hair follicles depressed and visible on its tense surface. If the beginning of such a wheal is not seen with the first pressure on the piston, something is wrong; the needle is withdrawn, the rest of the measured dose is injected into an adjacent skin area, and a tourniquet is applied above the two punctures. All this can be done quickly without alarming a patient who has been properly instructed.

If more than 0.17 c.c. is to be injected, it should be divided into two wheals, or the stronger solution employed. The tougher and less vascular skin of the outer surface of the arm or of the extensor region of the forearm is preferable to the thin skin of the flexor surfaces. Care is taken to avoid the locally desensitized sites of recent injections, for relief is proportionate not so much to the quantity of pollen extract injected, as to the extent and vigor of the local reaction.

So much insistence on technical detail may seem unwarranted, but in my experience such care and accuracy are necessary. The patient treated by this method cannot be turned over to the office nurse, with a set schedule. The physician has to decide each dose for each patient, and having done that, he may as well administer it.

After relief occurs, the interval between treatments is lengthened and the progressive increase of dosage continued up to a dose about double that which conferred relief. Certain patients disregard advice and take only one or two more doses after they obtain relief, and still escape a relapse. Some repeat this performance year after year.

RESULTS

My results have not been recorded in percentages. Based on the patients' reports and on my own observation of the objective symptoms and their disappearance, the result for each season has been classified as satisfactory or unsatisfactory. Thommen's definition applies here: "by 'satisfactory' the writer means the attainment of an adequate degree of comfort and relief, sufficient to enable the patient to continue his usual activities without hindrance, notwithstanding an occasional spell of symptoms." Many reported complete relief, but it should be borne in mind that a patient freed from most of the discomforts of a hay fever already established will render a more favorable verdict than one who, with the same degree of protection, had hoped

after weeks or months of preventive treatment to have no symptoms at all.

Two hundred and ninety-five patients, or 91.6 per cent of the patients, obtained satisfactory relief. Considered by seasons, the results in 508 seasons, or 93 per cent of the seasons, was satisfactory.

Relief, when obtained, was prompt. In 84 per cent of the satisfactory seasons, relief was reported at or before the end of seven days of intensive treatment. There were 14 seasons in which relief followed the intradermal test. This test was really the first dose, and it produced a sharp local reaction. To be considered with these are the 56 seasons in which the patient was comfortable after the first regular dose. Treatment was of course continued. The largest group, 210 seasons, reported relief after the second to the fourth dose, inclusive; 138 more by the time they had received the seventh dose. After that results were less gratifying, but in 90 other seasons the patients were relieved at or before the fifteenth dose. Results in the remaining 37 seasons, with long-delayed or partial relief or none at all, were classed as unsatisfactory.

The average patient required 14 doses per season. Several patients sensitive to a single pollen required only two doses after the test to check their symptoms for the year. In contrast to these were a group of multisensitized patients who required more than 40 doses a season to keep them comfortable. It was observed that in such cases a lesser number of doses was needed in each successive year of treatment. According to their response to intradermal therapy, these patients could be divided roughly into two groups. The greater number, with lively manifestations of pollinosis at the start, showed sharp local reactions to the treatments, with a large and irregularly spreading wheal which was soon surrounded by a wide area of bright erythema. After a few hours there was considerable swelling about the injection site; this swelling was likely to persist until the next day. Such patients did not tolerate or need a rapid increase in dosage; they obtained early relief while the type of their skin tests was still unchanged, and they showed little tendency to relapse.

On the other hand, there was a minority whose relief was accomplished and maintained only with difficulty. Their skin reactions were as a rule less intense; their dose could be increased more rapidly. Their relief came later, it was less nearly complete, and to maintain it the treatment had to be continued until the local reaction took on what might be called the protected type. That is, just as it does in the later course of effective preseasonal or perennial treatment, a large and fairly regular wheal, without pseudopods, followed the injection of the larger doses; the surrounding area of erythema was small, there was not much swelling, and the whole reaction vanished within a few

hours. In such cases it was necessary to work up to a dosage one-fourth to one-third as large as would be reached in preseasonal treatment.

CONSTITUTIONAL REACTIONS

There occurred in this series 12 general reactions; one to each 625 doses, or one in 45 hay fever seasons. These 12 reactions were experienced by 9 patients, so that one patient out of 36 had a pollen shock. Ten of the reactions were mild. One was severe, requiring two doses of adrenalin. It followed the injection of pollen extract into a skin damaged by eczema. The other reaction, less severe, happened because ten times the intended dose was administered. With its subsidence the patient's symptoms ended for that year.

Since the publications of Duke[3] and Insley[5] I have taught every new patient what to do if a reaction occurs, and have demonstrated the application of the tourniquet. While this precaution has not affected the incidence of general reactions, it has favored a bolder procedure in difficult cases. Certain patients who are known to be intolerant are protected by a tourniquet at each dose until relief is obtained; after that, they seem to lose their peculiar liability to pollen shock.

SKIN SCARS

Permanent blemishes on the skin were rarely seen, although bronzed discolorations fading after a week or so were frequent. The few permanent scars followed actual tissue destruction by scratching (not always in children), or they occurred to certain individuals whose skins were excessively irritated by glycerin. Unger and Moore[6] have recently commented on this irritant effect of glycerin when injected intradermally. In recent years I have used no dilution stronger than the 1:500, which, if made from a 1:50 extract in Stiers' solution, contains only 5 per cent of glycerin. For a few patients it was necessary to use a glycerin-free extract made by Coca's method. No adrenalin or ephedrin was mixed with the pollen extract; these vasoconstrictors favor necrosis of the skin.

The big local reactions are uncomfortable, but patients do not complain of them after they experience the relief that ensues. Indeed, they demand big reactions.

In this series of 7,500 pollen injections, no infections occurred.

THE FAILURES

Twenty-seven patients had 37 seasons in which the result of treatment was unsatisfactory: relief was partial, tardy, or absent. Three of these patients may be dismissed from consideration, being uncooperative. They did not give the treatment a fair trial. Five patients had one poor season apiece because of faulty diagnosis; an important sen-

sitization was missed or undervalued. After further study each of these five was completely relieved in the year following the failure. As to the others, the reason for failure seemed to reside in the patients themselves. Three were known to be peculiarly liable to pollen shock, and for this reason they were intentionally underdosed. One of them nevertheless suffered two of the general reactions noted in this series, but they were mild. In an earlier year he had nearly perished from the effect of a larger dose preseasonally.

There remain 16 patients with 20 unsatisfactory seasons in which the reason for failure is obscure. There was nothing found in their examination to differentiate them from the others of the multisensitized slowly reacting group who had relief from treatment. Their behavior is as puzzling as that of the 14 who were relieved by the intradermal test.

COMMENT

This report is presented with two objects in mind: the first, to add to the growing volume of evidence that hay fever and pollen asthma can be relieved during the attack. The method here presented works well under the conditions for which it was designed.

Its greatest disadvantage is found in the difficulty of its application. Intradermal pollen therapy demands of its user the utmost nicety of technic, a practiced judgment of dosage and reaction, and a knowledge of what pollens are on the air, and in what quantity. The difference between an ineffective dose and one that oversteps the patient's tolerance is not great.

The observation of Duke, that in his hands the intradermal technic was associated with scarring and, what was worse, with severe constitutional reactions, cannot be disregarded. He considered that the injection of concentrated extract into the skin, a tissue resistant to injections and well provided with venules and lymphatics, favored the rapid dissemination of the extract with shock promptly following. Since no local reaction followed the dose in his shock cases, he[7] believed that the injected solution entered directly a venule or a lymphatic channel. My own experience has been just the contrary. As stated in the earlier publication, I have found the intradermal route safer than the subcutaneous, for the reason that the injected extract can be watched as it forms the wheal; its absorption is retarded by the edema that promptly surrounds it. Any variation from this behavior can be seen at once, and proper measures used to check the absorption. In all of the general reactions recorded in this series there was a brisk local reaction, excepting the case in which the injection was made into eczematous skin.

As has been noted, vasoconstrictors and glycerin in the pollen extract favor skin blemishes. So do oversized injections; this method is not suitable for the larger doses of preseasonal treatment.

On the other hand, intradermal pollen therapy has certain advantages of its own. The total dosage is low, and nonspecific reactions in the presence of diseases such as tuberculosis do not occur. The average number of treatments is small, placing hay fever relief within the reach of persons of modest income. The treatment is effective at the time when relief is most demanded—during the attack. I have often used it successfully during attacks which a full preseasonal course had failed to prevent. One has the opportunity, in this method, to modify the plan of treatment according to the patient's need at that particular time. If a sensitization which previously had been overlooked, or undervalued, is preventing a satisfactory result, the inclusion of that pollen in the dosage brings relief which is prompt, and sometimes immediate. This quick relief from appropriate intradermal therapy is the second point I wish to stress.

A new patient may appear with reddened eyes, running nose, paroxysmal sneezing, perhaps with asthma. The intradermal test or (more usually) the first dose is administered, and the patient waits twenty or thirty minutes for observation. If that patient is among the fortunate 12 per cent, by the time the local reaction is fully developed the symptoms of pollinosis are noticeably abated; the eyes are clearer, the nostrils are open, the sneezing and wheezing cease. It is as if an injection of adrenalin had been made very slowly while the local reaction was developing.

Less dramatic but nearly as satisfactory is the lessening of symptoms which in favorable cases follows each daily dose, until at the end of a week four-fifths of the patients are so comfortable that it is necessary to advise them not to invite a relapse by stopping treatment.

Such prompt relief does not, in my experience, follow the administration of pollen extract into muscle or fat; it seems to be related to the reaction in the skin. It is not a mechanical reflex, for the injection of the same quantity of an extract to which the patient is not sensitive has no effect. The quantity of pollen substance contained in the earlier injections is infinitesimal, and even at the end of treatment by this method the quantity injected is small—too small, one would think, for an antigen-antibody effect. What seems to happen is a partial or complete correction of the disordered physiology of the allergic, a change toward the normal way of dealing with inhaled pollen. Whether, as some suppose, sugar is released into the blood from the liver; whether the adrenal glands increase their output, or whether some enzyme resembling histaminase is liberated, can only be conjectured. The phenomenon occurred in about 12 per cent of my cases, and it was elicited year after year. It is described here in the hope that some one equipped for research will undertake its investigation. Such research, if successful, might throw light on the factors underlying the allergic state.

SUMMARY

This paper reviews the records of 322 hay fever patients, with an aggregate of 545 hay fever seasons, who were treated during the attack by the intradermal injection of pollen extract.

The work was done in central Arizona, where the pollinating season is nine months long, and climatic conditions favor the anemophilous plants.

The technic of injection and the method of determining the proper dose for each individual at each treatment are described. More than 91 per cent of the patients, in 93 per cent of the seasons, obtained satisfactory results.

Relief, when obtained, was prompt, usually occurring at or before the end of seven days of intensive treatment.

There were 12 general reactions, distributed among 9 patients; a proportion of one general reaction in 45 seasons, or one to each 625 doses. Only two were severe; none was fatal.

The few permanent skin blemishes seen were caused either by scratching, or by the intolerance of certain skins to the glycerin in the injected solutions.

Intradermal pollen therapy offers an effective method for the relief of hay fever and pollen asthma during the attack.

Its successful use requires the utmost nicety of technic, a practiced judgment of dosage, and an accurate knowledge of the local pollen picture. Its special advantages are the low dosage required, the low cost to the patient, and the promptness with which relief occurs.

The phenomenon of almost immediate relief, which in certain cases follows one of the first intradermal injections, merits further investigation.

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AIR CONDITIONING AS A MEANS OF REMOVING POLLEN AND OTHER PARTICULATE MATTER AND OF RELIEVING POLLINOSIS*

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IN 1924 Van Leeuwen[1] described an apparatus for removing allergens from the air. Atmospheric air was drawn into a tube 115 feet high and passed through a refrigerator with cooled pipes. The allergens were removed with the moisture which collected on the pipes, and the air was then passed into an allergen-free chamber. In 1925 Leopold and Leopold[2] described an apparatus which forced air through a water spray thus removing the allergens. Later Cohen[3] described a filter of woven wool and cotton through which air was passed. This filter was shown to be over 99 per cent efficient for pollens 10 or more microns in diameter. Recently Peshkin and Beck[4] described a simpler type of filter made of layers of cellulose which could be fitted into any window. He introduced 0.17 gram of ragweed pollen, which represents about 65,000,000 grains of pollen, into the filter and not a single pollen was found on vaselined slides held over the outlet. None of these filters have been ideal. Patients have complained of noise, or in the hot weather of the heat and stuffiness of the room. Also the filters must be changed frequently.

Recently air conditioners have been installed in theaters, offices and homes. This study was undertaken to determine whether the air conditioner, which does not have the disadvantages listed above, would be of value in removing pollens from the air. A recent report was made by Gay[5] on the treatment of hay fever and asthma in air-conditioned atmosphere. He found that patients were completely relieved from hay fever within a few hours and the cases of pollen asthma were relieved in twelve hours.

The standard Frigidaire air conditioner was set up in a room at Johnston Willis Hospital, Richmond, measuring 12 feet by 15 feet, and 9 feet high with a total volume of 1,620 cubic feet. Four hundred and fifty cubic feet of air pass through the air conditioner per minute. Thus it takes only 3.6 minutes for the total amount of the air in the room to pass through the conditioner. This was a corner room with two windows and no special precautions were taken against

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the ingress of pollen except that the windows and door were kept closed at all times. The plan had been to use the air conditioner throughout the ragweed pollen season, 1932, but owing to a delay in completing the set-up observations were not started until September 6. This was the date of our maximum pollen prevalence during the 1932 ragweed season, and the observations were therefore limited to that period representing the descending limb of the ragweed curve.

The conditioner is contained in a steel cabinet measuring 28¾ inches wide, 14 inches deep and 42⅝ inches high. Air is drawn in from the room through an opening at the bottom of the conditioner by means of two centrifugal-type fans. It is passed over spiral finned copper pipes within which flows the refrigerant. The air is cooled and moisture from the room collects on the pipes. A grille at the top of the conditioner is so shaped that the air is forced out at an angle of 70 degrees from the horizontal. The moisture on the pipes drops down and is carried away through a drain. It will be shown below that particulate matter including pollen granules is taken out of the air with this moisture. Two ⅜ inch pipes serve to carry the refrigerant to and from the conditioner. A special compressor automatically controlled according to temperature requirements cools and forces the refrigerant through the conditioner. It is not necessary that the compressor be in the air-conditioned room.

During the period, September 6 to October 4, in which ragweed was in the air, comparative counts were made at three stations. The first was in the air-conditioned room, the second in the next room, not air conditioned, and the third on the outside window sill of the second room. Ordinary microscope slides smeared with a thin coating of vaseline were exposed in these three locations for periods varying from one to nine days, the exposure being of the same duration each time in all three locations. The ragweed pollen deposited on the slide in the air-conditioned room was so scarce that, even after several days' exposure, only a very few grains were discovered even after the entire surface of the slide had been searched (18.75 square centimeters). The area counted on slides from the other two stations represented 1.75 square centimeters and this was multiplied by the factor 10.7 for comparable readings.

It will be seen from Table I that the pollen count in an ordinary hospital room in which no precautions were taken with regard to door and window, always ranged decidedly lower than the count for outside air. The counts in the air-conditioned room were extremely low compared with the nonconditioned room. For a total pollen count in the outside air, of 11,728 during the period of study, there were only 19 grains deposited on the same sized area in the conditioned room. Counts were not available for all of the periods in the nonconditioned

room, since unfortunately this room was occupied and for one reason or another the slides were misplaced or spoiled. However, taking the periods in which counts were made at all three stations, for a total deposit of 6,303 pollen grains from the outside air there were 1,476 in the nonconditioned room and 6 in the air-conditioned room. Comparing the two rooms, we may say that 99.593 per cent of the pollen was removed or excluded in the conditioned room.

Table I also shows that under the conditions of the experiment an ordinary room lost 76.6 per cent of the pollen concentration of the outside air, while the conditioned room lost 99.7 per cent. Or we may say that an ordinary room has 23.4 per cent as much pollen as outside air while the conditioned room had 0.3 per cent.

TABLE I

RAGWEED POLLEN DEPOSITED ON SLIDES DURING THE POLLEN SEASON

DATES	NUMBER OF DAYS	OUTDOORS	IN NONCONDITIONED ROOM	IN CONDITIONED ROOM
Sept. 6	1	1,188	407	2
Sept. 7, 8	2	1,926	No count	0
Sept. 9-12	4	963	No count	4
Sept. 13-15	3	1,434	No count	0
Sept. 16-18	3	1,402	246	4
Sept. 19-21	3	214	21	0
Sept. 22-25	4	3,499	802	0
Sept. 26—Oct. 4	9	1,102	No count	9
Total for all days		11,728		19
Total for days in which nonconditioned room counts were made		6,303	1,476	6

The conditioner was installed too late in the season for extensive clinical observation. It is our intention to continue this portion of the study during the next pollen season. One patient who had had what is usually inadequate preseasonal desensitization, with a top dose of 0.2 c.c. of 2 per cent ragweed extract, had very little relief during the first half of the pollen season. This patient spent the night of September 7 in the conditioned room. The pollen count for September 7 and 8 was zero in the room. The patient was not relieved during the night in the room. Unfortunately, however, she was sensitive to feathers and through inadvertence slept on a feather pillow in the conditioned room. No conclusions therefore can be drawn from this case.

The second patient had a severe hay fever and had had no treatment prior to spending three days and nights in the conditioned room (September 20, 21 and 22). During this period the room counts were zero. The patient had had an unusually severe hay fever with considerable edema of the nasal mucosa. At the end of twenty-four hours in the room she considered herself to be about 25 per cent improved. At the end of the second day she was 50 per cent improved, and at the end of

the third day she considered herself to be 75 per cent relieved. After leaving the conditioned room she remained 75 per cent relieved for forty-eight hours in spite of the fact that the pollen count for Richmond during the first twenty-four hours was reasonably elevated for this vicinity (60). After forty-eight hours she suffered a return of her hay fever for two days during which the atmosphere pollen count was 21 and 19 per cubic yard of air. The patient was then placed on coseasonal ragweed desensitization with what she estimated at 75 per cent to 80 per cent relief.

The observations so far would indicate that the pollen content of the air-conditioned room is reduced almost to zero and that the concentration was sufficiently low so that one patient obtained as much relief in the room as she did from coseasonal desensitization.

The low concentration may be attributed to either or both of two factors: the closing of the windows and doors, and the removal of the pollen by the air conditioner. Pollen had been purposely excluded from the room as far as possible, and this fact undoubtedly played a great part in producing the low pollen count. However, during the heat of August and early September such a closed room without cooling and washing of the air as is provided in the conditioner would be hot, stuffy and unpleasant. The temperature of the conditioned room ranged 10 degrees lower than that of adjoining rooms and the air was fresh and pleasant. The room was very comfortable.

We next attempted to determine whether the conditioner actually removes pollen grains and other particulate matter from the air circulating through it.

Lycopodium is a fine powder which does not dissolve in water at ordinary temperatures and the spores of which are about the size of the average pollen grain. It has a characteristic microscopic appearance making it possible to count the spores. Fifteen grams of lycopodium were distributed through the air of the room, using a hair dryer type of motor blower. Air samples were taken ten minutes later and at intervals thereafter. The air was drawn for fifteen seconds through a Polar Cub vacuum cleaner and blown against a vaselined slide attached 6 cm. from the outlet, vaselined surface toward the air current. The tube of the microscope was set at 162. The grains were counted five times across the width of the slide with the low power field. The total number of grains was recorded.

TABLE II

10:30 A.M.	Powder introduced into the air
10:40 A.M.	9452 grains
11:10 A.M.	830 grains
11:40 A.M.	272 grains
12:40 P.M.	285 grains

At this point it was noticed that a considerable portion of the lycopodium had settled to the floor. Three fans were placed on the floor and an attempt was made to recirculate the lycopodium. Counts were made of the air which had passed through the conditioner by holding a vaselined slide over the outlet for fifteen seconds.

TABLE III

	ROOM	AIR CONDITIONER
1:10 P.M.	945	181
3:15 P.M.	572	167
5:45 P.M.	261	97
10:30 A.M. second day	318	142

The water of condensation from the conditioner was collected during the entire experiment, and 0.995 gram of lycopodium was recovered from it. An unweighed quantity of ragweed pollen was introduced directly into the conditioner intake. The water of condensation was collected from the outflow tube in a pan. The pollen was easily seen grossly as a light scum on the surface, and microscopic examination of the water showed large numbers of ragweed pollen granules. This apparatus is not adapted to a quantitative recovery of particulate matter. The observations do show, however, that spores and pollens are removed in the water of condensation.

According to Scheppegrell[7] there are 380,000,000 pollen grains of short ragweed per gram. Two-tenths of a gram, or 76,000,000 ragweed pollen grains, were introduced three different times into the intake of the air conditioner. Vaselined slides were held for two minutes each over the outlet, which had been tapered down to an area of 30 square centimeters. The area of the slide counted was 1.778 square centimeters.

TABLE IV

RAGWEED POLLEN PASSING THROUGH CONDITIONER AFTER INTRODUCTION OF 0.6 GM. INTO INTAKE

First slide	543 grains
Second slide	803 grains
Third slide	717 grains

Two minutes appeared to be sufficient time to allow passage of whatever pollen grains were not deposited on the moist coils. Assuming that all pollen blown against the face of the vaselined slide remained deposited thereon, we may calculate from the area of the slide and that of the entire outlet, that the total number of grains escaping through the conditioner averaged 12,384. The average relative humidity for these experiments was 55 per cent with the temperature varying from 68° to 71° F.

The conditioner was stopped and the room kept closed for one month. After this interval numerous lycopodium spores were demonstrated in the dust on the floor and furniture. The conditioner was again started. Three grams of ragweed, representing approximately one billion grains, were blown into the air. Fans were placed on the floor to keep the pollen in the air. Counts were made ten minutes later and at daily intervals thereafter.

TABLE V

POLLEN AND SPORE COUNTS IN THE AIR AND AFTER PASSING THROUGH THE CONDITIONER

	AIR IN ROOM		OUTGOING AIR FROM CONDITIONER		DEPOSITED ON FLOOR	
	COUNTS PER MINUTE		COUNTS PER 24 HR.		COUNTS PER 24 HR.	
3 grams ragweed introduced into air	Lyco.	Ragweed	Lyco.	Ragweed	Lyco.	Ragweed
10 minutes later	155	1535				
Relative Humidity 60% to 65%; Temp. 69° F.						
2nd day	50	35	640	1010		
3rd day	50	102	330	51		
4th day	120	85	235	85		
5th day	112	80	140	25		
6th day	95	67	135	70		
7th day	45	20	90	15	1110	380
8th day	640	152	30	95	----	---
9th day	23	13	10	5	80	70
10th day	110	47	5	0	5	25
11th day	82	20	--	--	65	45
12th day	55	12	5	0	0	0
Humidity Increased to 96%–98%; Temp. 68°–69° F.						
29th day	65	22	--	--	--	--
30th day	50	10	55	5	5	0
31st day	25	2	38	9	9	1

The daily counts recorded in Table V, up to the twelfth day, were made in an average humidity for the season (March). After the twelfth day the conditioner was stopped and the room kept closed. The humidity during the ragweed season is usually decidedly higher than it was during this portion of the experiment. The conditioner theoretically will remove particulate matter more effectively in the presence of a higher humidity, since under these conditions more moisture accumulates on the cold coils. Seventeen days after the termination of the first portion of this experiment it was therefore continued, with an artificially induced high humidity obtained with the use of Hot Point Humidifiers. Unfortunately the observation of this period was necessarily discontinued at the end of three days when as a result of the high humidity water commenced to accumulate on the walls and ceiling.

Table V shows distinct variations in the daily count, but very definite conclusions may be drawn therefrom.

The fans, placed on the floor, were directed horizontally, thereby stirring up the dust on the floor. They were nonoscillating fans. The high room count on the eighth day was probably due to changing the position of a fan. Obviously, not all of the spores and pollen were kept in the air and many must have settled down. However, beginning with the sixth day, twenty-four-hour slides were exposed on the floor at different places in the room to determine how much pollen was actually settling out from the air each day. The last two columns in Table V indicate a gradual diminution in the amount of pollen settling out of the air each day. The unusually high counts on the seventh day were presumably due to carelessness in placing the slide, by slipping it along the floor, thereby stirring up considerable floor dust in its immediate vicinity.

The figures in columns 1 and 2 indicate the number of spores and pollen granules deposited on the slide in one minute's time by means of a motor blower similar in principle to that recently described by Duke[6] for obtaining rapid pollen counts. This same motor (Polar Cub) was used in obtaining the room air count for the quarter minute periods described in Table III.

The figures in columns 3 and 4, Table V, represent twenty-four-hour deposits on the slides faced against the outlet of the conditioner. The air sample counts in columns 1 and 2 are averages of counts obtained from various parts of the room, particularly at about the center of the room at a height of three feet from the floor, and from near the intake of the conditioner.

We may interpret these figures as follows: On the sixth day, for example, 95 lycopodium spores per unit area on the slide were collected by means of the blower in one minute's time. The same air after passing through the conditioner deposited only 135 spores per unit area after twenty-four hours. While 67 ragweed granules were deposited from the room air in one minute, it took twenty-four hours for approximately the same number (70) to be deposited from the air as it left the conditioner. We may infer therefrom that most of the spores and pollen granules were removed in the conditioner. The diminution in the number of granules settling out on the slides placed on the floor would also indicate that they had been washed out of the air.

The results for the last three days, particularly those recorded in columns 1 and 2, suggest that the increased humidity increases the effectiveness of the conditioner in removing particulate matter, although the wide variation in the count for preceding days detracts from the conclusiveness of the record.

CONCLUSIONS

1. The concentration of ragweed pollen in an air-conditioned room with the door and window closed during the latter part of the 1932 ragweed season was almost zero.

2. Clinically, relief of symptoms of hay fever occurred in an air-conditioned room in one of the two patients observed.

3. Experimentally, when lycopodium spores and ragweed pollen were introduced into the air-conditioned room: (a) the concentration in the air of both spores and pollen was gradually reduced to zero (this was not due to settling out of the spores and pollens); (b) the pollen and spore concentrations were much higher in the air in the room than corresponding counts taken from the air coming out of the conditioner; (c) appreciable amounts of both spores and pollen were filtered out of the water of condensation from the air conditioner.

4. The experimental evidence is favorable enough to warrant further clinical studies of the air conditioner.

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THE ANTIGEN-FREE* ROOM IN THE DETECTION AND CONTROL OF CUTANEOUS ANERGY IN POLLEN BRONCHIAL ASTHMA†

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THE failure of skin tests done intradermally with serial pollen extract dilutions to invariably parallel clinical sensitivity in pollen hay fever and asthma is now widely recognized.[1] Attention has been called elsewhere to such almost routine cutaneous refractoriness in very ill cases of pollen bronchial asthma,[2] and in addition, in cases due to a low degree of pollen sensitivity where 1:50 or even 1:10 dilutions will only occasionally give the clinically indicated positive results, and where even the pure pollen conjunctival test occasionally fails us.[3] A pollen-free* environment, of course, easily gives us the diagnostic clue in these cases.

The purpose of this article is to call attention to this condition of cutaneous anergy, temporary or permanent, partial or complete, in another group of patients who will not fit in either of the above classifications, in whom failure of recognition of the true state of affairs postpones proper desensitization efforts, and the advantages of an antigen-free room in the recognition and control of skin refractory pollen asthma cases in general.

The following represents a typical seasonal moderately sensitive pollen case with cutaneous anergy:

Mrs. W. A. W., aged thirty-two years, living for many years on a farm fifty miles northeast of San Antonio, was seen August 25, 1932, giving a history of almost daily asthma of some three months' duration, the twelfth year of such seasonal summer and fall recurrence, requiring epinephrine about once a week, with an increase in severity in September and early October; a typical southwest Texas moderate amaranth asthma story. She was tested the previous year by Dr. D. H. Hotchkiss, Jr., of Houston, giving only a slight positive reaction when an intradermal 1:20 extract was reached.[4] All of our tests including 1:500 extracts were negative, and the pure pollen ophthalmic test also was negative. Under the natural assumption that this was one of our usual low degree sensitivity cases, the following intracutaneous treatment was instituted, and the results are appended. There was no

*The terms "antigen-free" and "pollen-free" are, of course, used in a relative sense. All known specific and nonspecific antigens (dusts, odors, temperature changes) are eliminated as far as humanly possible. Atmospheric pollen factors are controlled by the constant use of mechanical filtration of proved efficiency. Our absolute antigen-free control actually is about 95 per cent to 98 per cent.

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specific cutaneous response to any individual treatment, the initial papule disappearing promptly, no wheal formation, and only transitory erythema, nothing beyond the expected results of a similar-sized control injection.

August 27 Amaranth 0.02 c.c. 1:500 intracutaneously, asthma improved.
August 29 Amaranth 0.04 c.c. 1:500 intracutaneously, asthma improved.
August 30 Amaranth 0.01 c.c. 1:50 intracutaneously, three doses of epinephrine required that night.
September 2 Amaranth 0.01 c.c. 1:50 intracutaneously, asthma continuous for three days.

Specific treatment was then omitted for twelve days, the asthma gradually returning to its original basis. The diagnosis of extreme low degree sensitivity was obviously untenable.

On September 14, amaranth 0.01 c.c. 1:5,000 was given intracutaneously with immediate improvement. The asthma cleared completely under weekly dosages gradually raised to 0.02 c.c. of 1:500, beyond which there was no tolerance. (Untreated amaranth cases in southwest Texas do not start to clear spontaneously as early as September 16, as this case did.)

This patient was retested preseasonally in March, 1933, when clear, and found negative to amaranth and other concurrent pollens of her environment (ragweeds and grasses) by skin tests, pollen ophthalmic tests and passive transfer. During subsequent routine preseasonal subcutaneous desensitization, the first sign of light asthma produced by treatment occurred twenty-four hours following the March 16 dose of 0.06 c.c. of 1:50, and subsequently twice on slightly smaller doses. There was no local arm reaction with this or any previous dose. The reason for the cutaneous anergy in this case is unknown, and until clinical study revealed the true state of affairs, the only sign of overdosage other than the subsequent asthma (no hay fever of any note and no urticaria or skin itching) was an accelerated pulse noticeable to the patient within a few hours.

That we have a means for revealing this condition in these moderately sensitive cases, as well as in the low degree sensitivity or very ill patients, by means of an antigen-free room is shown by the following case:

Miss P., aged sixty-nine years, was seen January 1, 1931, with a history of asthma of about ten days' duration, corresponding with the onset of our Texas mountain cedar *(Sabina sabinoides)* season. This patient was an old summer-fall pollen case of Dr. C. H. Eyermann of St. Louis, visiting at the time in San Antonio, and when she was first seen by us, was taking epinephrine several times daily. Cedar dermal tests were negative. Between January 1 and January 27, 1932, an attempt was made to diagnose and coincidently desensitize this patient with coseasonal intradermal cedar extract treatment, the dosage being

raised from 0.02 c.c. of 1:5,000 gradually up to 0.02 c.c. of 1:50, using a different section of the body for each injection in the usual manner, with absolutely no skin reactions to any dose, and with absolutely no clinical improvement. She was then placed in an antigen-free room, previously refused. After a week's stay without treatment beyond required epinephrine, the asthma cleared. This patient was then retested intradermally, showing a distinct immediate ++++ reaction to mountain cedar, 0.02 c.c. of a 1:5,000 extract, where during the previous anergic state, she had a completely negative test to 0.02 c.c. of 1:50, a dose one hundred times larger. That the anergic state did not include other pollens to which the patient was clinically and cutaneously sensitive, is shown by the fact that during the period of cedar skin refractoriness, she showed ++++ positive reactions to both ragweed and carelessweed in the usual testing strength dilutions.

Subsequent management of this case by specific coseasonal intradermal treatment based on the detection of the true degree of sensitivity, gave excellent results, permitting a gradual relaxation of pollen precautions. The final dose of mountain cedar given February 17, 1931, was 0.01 c.c. of 1:500 intradermally (cutaneous reaction +++ positive), the season terminating about one week later. The original cutaneous refractoriness in this case obviously rested on some immunologic basis.

The suggestion may be offered that, after all, epinephrine is the real reason for the blockage of the skin response, at least in a certain number of these skin refractory asthma cases. Granted that this be undoubtedly true, an antigen-free room certainly furnishes an excellent means for determining this fact by removing the necessity for the use of such material.

It is admitted that only a limited number of allergy workers use the intradermal ceseasonal method of treatment, and technical dosage details of the cases quoted are thus of limited interest, except as applying to routine testing. It is also admitted that in many clinics the very ill patients of pollen bronchial asthma are recognized as unfit for immediate thorough testing. But the practice of thorough coseasonal testing of the average hay fever and asthma case up to the point of definite diagnostic wheal and pseudopod formation is still practically universal.

Rackemann,[5] as far as we can make out, was the first worker to publish a case report and conclusion showing the far greater potency of intradermal as compared with subcutaneous pollen dosages, securing a constitutional reaction with an intradermal dosage one-tenth the size of the previous subcutaneous dosage which had produced merely a "not excessive local reaction." He also calls attention to the smaller dosage requirements in general of intradermally treated pollen cases.

This finding, after several years' experience with routine coseasonal intradermal treatment, we can fully corroborate, estimating this ratio biologically to be about eight or ten to one. If these findings are accepted as correct, then it becomes at once perfectly obvious that each intradermal test in every case represents not only a test, but the equivalent of a subcutaneous dosage approximately eight or ten times greater, and one potentially of appreciable size for that particular individual at that particular time. We have seen many temporary relapses, several of considerable severity, in intradermally tested positive skin test cases of both hay fever and asthma, usually coseasonally tested, even in patients beginning to improve in antigen-free rooms, where consideration was not given to the ability of the patient to tolerate constitutionally for the time being, the skin reaction producing dosages.

In even preliminary dermal testing, especially when coseasonally performed, it is routine in our office to consider each positive test a dose of antigen as well, and to withhold all subsequent intradermal tests or specific treatment until such dermal reaction completely disappears.

In these skin refractory cases, the inability of the patient for the time being, from either anatomic or immunologic reasons, to give the usual skin response, naturally at times leads to the diagnosis of relative insensitivity, and the expectation of its proof by the use of extracts of higher concentration. In certain instances this, of course, is the correct condition and procedure. In others of high sensitivity with cutaneous anergy, disregard of this idea, with coincident antigen dosage reception beyond the patient's true clinical tolerance, results only in relapse or, at the best, in delay in the resolution of the hay fever or asthma state. Diagnostic differentiation here, of course, is admittedly difficult, calling for the exercise of considerable care and judgment, but, as will be seen later, not impossible if certain guiding factors are employed.

Delayed, light, and modified constitutional reactions from overdosage in pollen desensitization treatment in patients giving the usual skin response have been recognized, of course, for many years.[6] In the same manner, in these skin refractory cases of pollen bronchial asthma of all grades of severity, treatment overdosage causes constitutional symptoms in the shape of and limited to respiratory distress which are not always immediate, but occasionally have an inception delayed even for twenty-four to forty-eight hours. Such delayed preliminary symptoms for the first two or three days may be mild and purely nocturnal, and may retrogress from that stage, provided cutaneous anergy is promptly recognized. Nonrecognition of this point, and the ascribing of symptoms to underdosage, concurrent specific or nonspecific factors, with dosage persistence, leads to the severest type of intractability, particularly when coseasonal.

In some of these coseasonally overtreated pollen cases, especially if they be originally of the severe chronic intractable type, the above mentioned retrogression will not occur, and symptoms will gradually increase to a continuous stage of moderate to extreme severity. In these cases, an antigen-free room is absolutely indispensable. Otherwise, symptoms will persist throughout the season, and possibly for an appreciable period thereafter. Even with an antigen-free room, occasionally in cases of this class, many, and not a few, days will be required for clearing, the room thus giving us in overtreated cases additional diagnostic information as to type with regard to the capabilities of antigen elimination and a guide for subsequent dosage sizes and intervals.

In purely coseasonal cutaneously anergic cases of both hay fever and asthma, the date of the initial symptoms, whether appearing immediately with the very initial seasonal appearance of the offending atmospheric pollen, or whether delayed for several days or weeks thereafter, whether present only during periods of high wind velocity and heavy pollen concentration, or only during periods of excessive pollen contact opportunity, the amount of symptom relief medication required, are, of course, all valuable corroborating clinical factors assisting to reach a conclusion on the points of degree of sensitivity and proper specific dosage testing and treatment inception.

In chronic bronchial asthma, the history, general condition of the patient, pollen environmental observations, relief medication requirements, and possibly the degree of blood eosinophilia, are similar guides. But above all, the most important information along these lines is that derived from the length of time required for these patients to improve and become symptom free in an antigen-free room where their spontaneous resolution has not been interfered with by usual routine intradermal testing, followed by careful observation of the results, immediate or delayed, of properly spaced intradermal dosages, beginning with extracts of such minimal concentration as are consistent with the presence of a condition of extreme hypersensitivity existing often, at least temporarily, in these cases.

Assuming the absence of infectious sinus or pulmonary complications, the pollen-free room gives us an excellent means for diagnosing the real clinical sensitivity of these skin refractory, and in fact of all, pollen bronchial asthma cases, and the subsequent institution of proper specific treatment dosages. Cases with a high degree of resistance, from an immunologic point of view, will clear within twenty-four to forty-eight hours. The average case will become symptom free within a week.

However, the idea that the strictest kind of an antigen-free environment, including due regard to ordinarily known dietary and all known

specific and nonspecific antigens, should invariably clear an uncomplicated pollen asthma within a few days should be disregarded. From our experience in handling constantly in a health resort an unusually large percentage of negative skin test, heavy daily epinephrine using, almost intractable pollen bronchial asthma patients, it has been our observation that while improvement in the shape of appreciable reduction in antispasmodic remedial requirements will be practically invariably attained within a ten-day period, weeks, and at times months, will be required for total clearing, not in a few but in many cases of this type.[2] Following the ordinary leaving of the near-perfect hospital room, for economic reasons, identical results ensue even from pollen precautions, mechanical filters, etc., in the less perfect home environment.

The early clearing cases are suitable for prompt, specific testing and for treatment in the usual manner even with cutaneous anergy. In the very ill, chronic patients, specific testing and treatment, as before mentioned, result only in relapse even with the more minute dosages. And, of course, there are many intervening grades. The notation of symptom increases within twenty-four to forty-eight hours following specific testing beginning with very high dilutions and spaced infrequently enough to gauge this point, will indicate the correct clinical sensitivity, and determine proper specific dosages and intervals. Errors of judgment so derived are, of course, possible, but in experienced hands the results should be of limited severity and only temporary.

We use routine cytologic examinations of the nasal smear as a guide in all our asthma cases. In the presence of a constantly predominating high nasal smear eosinophilia, even in the face of the complete cutaneous refractoriness so often existing, the condition is considered specifically allergic and is handled purely on this basis, no matter how many weeks may be required for clearing. The point is, that these cases do eventually clear, though months may be required.[7] Even our cases of asthma with frank, obvious paranasal sinus suppuration are considered primarily of specific nonbacterial origin and placed under the same régime; though appropriate treatment for such complication is, of course, used where indicated.

Taking into consideration and allowing for this point of the real time element needed to take care of the protracted delay in clearing in our very ill patients with chronic asthma, along with the almost routine use of an antigen-free room in some form in skin refractory patients not necessarily so ill, have reduced our percentage of nonspecific, reflex or bacterial asthma cases to practically the vanishing point, environment studies subsequent to clearing giving us the correct specific diagnosis in spite of the cutaneous anergy, which specific diagnosis in our community is almost invariably pollen.

All of us have seen patients with seasonal hay fever and asthma in whom recognized or unrecognized overtreatment has produced intractable symptoms lasting the balance of the current season, and not controllable either by treatment dosage changes or by complete treatment withdrawal, especially where partial cutaneous anergy inhibits the real actual skin response clinically indicated.

In these cases both of hay fever and asthma, a pollen-free environment, by removing the interference of current atmospheric pollen will in a few days, as a rule, enable these patients to become symptom free, permitting correct treatment resumption and correcting what would otherwise be certain seasonal failure. While it is readily admitted that but few patients with hay fever can be persuaded to go to a pollen-free hospital room, still it is practicable and acceptable to many of them to use downtown, inside court, hotel rooms, or purchased or loaned mechanical filters at home. A few days' stay at the seashore occasionally makes a good substitute. We have cleared many of these cases in two or three days by keeping the patient all day in a small pollen-free room connected with our office, at times under epinephrine, followed by sleeping at home with closed windows. Withholding of all specific treatment temporarily until clearing occurs, as it invariably does under such management, followed by its resumption beginning with initial weak dilutions, has almost universally given splendid results for the balance of the season in these cases that otherwise would have been total failures.

It is our opinion after some ten years of experience with homemade and commercial pollen filters that the antigen-free room is an absolutely indispensable part of the armamentarium of the allergy worker. In fact, we were using homemade filtering apparatus of high filtration efficiency several years before mechanical pollen filters appeared commercially.

There is no reason why the principles here discussed should not be equally applied to preseasonal and coseasonal subcutaneous specific treatment dosages. While it is perfectly true that a local injection site cutaneous reaction usually indicates the approach of impending constitutional tolerance limit for the time being, the converse is not by any means invariably true. We have on numerous occasions witnessed immediate or delayed overdosage nasal or pulmonary symptoms in the course of routine preseasonal desensitization in the face of absent or minimal local skin reactions. This experience, of course, is not unique.

In conclusion, the securing of no reaction or of only minimal skin reaction from intradermal tests and from specific pollen treatment, both preseasonally and coseasonally done, in proved pollen bronchial asthma cases does not invariably necessarily indicate, as might rather be presumed, relative insensitivity or insufficient specific dosage.

The antigen-free room is of decided advantage in recognizing and controlling these not uncommon cases of cutaneous anergy accompanying bronchial asthma of atmospheric pollen etiology.

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NEURODERMATITIS DUE TO PROTEIN SENSITIZATION*†

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THE term "neurodermatitis" was first used by Brocq to designate a clinical skin entity to which numerous other terms have been applied before and since Brocq published his views. It is our aim here to present briefly the salient features of this condition and to report our observations which together with the studies of Wise and Ramirez,[1] Rost,[2] Haxthausen,[3] Urbach,[4] Biberstein,[5] Sulzberger,[6] and others, would seem to place neurodermatitis in the class of allergic dermatoses.

The various chronologic phases leading up to the present-day status of neurodermatitis was recently minutely described by Alexander.[7] It appears that the first to describe this condition was Willan in 1808 under terms that have long since been discarded. Likewise were discarded the various terms applied to this condition by Bateman, a pupil of Willan, Besnier, Jacquet, and Bodin. Vidal described the circumscribed type of neurodermatitis under the term "*Lichen Simplex Chronicus.*" This term persisted in spite of the fact that it is confusing The neurodermatoses are not lichens even though occasionally a patch of lichenified neurodermatitis may simulate lichen planus. The term "lichen" should be reserved for the group of true lichen dermatoses such as lichen planus, etc. Brocq, a pupil of Vidal, coined the term "neurodermite" to characterize this disease because of its association with extensive itching and nervousness, but without any desire to imply an immediate causal involvement of the central or peripheral nervous system. It is for this reason, too, that he subsequently abandoned the term "neurodermatitis" as misleading, and substituted the words "pruritus with lichenification."

Not all dermatologists accept neurodermatitis as a disease *sui generis.* Many of the older American and German dermatologists consider neurodermatitis as a chronic papular eczema, although adding that it is "a characteristic symptom complex, which deserves at least nosological identity." But with very few exceptions the majority of present-day dermatologists agree with Brocq and accept neurodermatitis as a definite clinical entity different from eczema in its clinical course and pathologic appearance.

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The classical descriptions of the lesions of neurodermatitis by Brocq have not, as pointed out by Wise,[8] been sufficiently read and studied. This accounts for some of the confusion and controversies that one meets sporadically in the literature.

MODE OF APPEARANCE OF THE CUTANEOUS LESIONS (WISE)

At the outset there is absolutely no visible lesion on the integument; gradually the tissues change as a result of scratching; they first lose their normal color and assume a slightly dusky and at the same time, pinkish tint; on close inspection the skin is seen to present a finely granular and mottled appearance. At this stage it is already possible to discern in certain localities, under varying illumination, a sort of flattened, poorly outlined, somewhat glistening, very minute pseudopapule formation. Later on these lesions become more pronounced, the tissues assuming a dusky red color or becoming distinctly pigmented; they are roughened and begin to be furrowed by fine criss-cross lines. The dermis gradually thickens, becomes infiltrated, and the disease finally assumes a truly pathognomonic appearance.

This process, pruritus-scratching-pseudopapule formation—lichenification may be limited only to one patch, to a number of circumscribed patches or may be diffuse and occupy entire segments of the body and occasionally even the entire body. This disease favors certain areas, such as the arms, forearms, the thighs, the upper portion of the thorax, the back, the face and especially the forehead, the malar prominences and the cheeks. The attacks of pruritus are usually intermittent, paroxysmal, and vary with the seasons of the year. Coexisting with this diffuse type of neurodermatitis are occasionally patches of the circumscribed type of neurodermatitis.

As a rule, after an active stage which may last from a few weeks to several months, the affection shows a tendency to disappear through gradual diminution of the pruritus, cessation of the scratching, and healing of the lesions. But the relief usually lasts only a short time and a recurrence follows, repeating the same process of itching, scratching, lichenification.

HISTOPATHOLOGY

The histopathology of neurodermatitis has been studied by Brocq and Jacquet,[9] Kreibich,[10] Ehrmann,[11] Alexander,[7] Highman,[12] and others. (There is almost unanimous agreement in the main findings.)

According to Highman the salient histopathologic characteristics of neurodermatitis are: parakeratosis and hyperkeratosis, with intercellular edema of the rete pegs; acanthosis in the rete pegs causing an elongation of the latter. Subepidermal accumulations of serum, hypertrophy and edema of the papillae. The papillary vessels are

dilated, and there is an infiltration of the papillae with lymphocytes, fibroblasts, and a few mast cells. Infiltration of cells about the vessels forming foci and edema and hyperplasia of the collagen.

The microscopic differentiation between neurodermatitis and eczema consists in the absence of vesicle formation in the epidermis.

ETIOLOGY

When Brocq termed this condition neurodermatitis, he did not wish to imply an immediate causal involvement of the central or peripheral nervous system. Brocq, however, observed that some of his patients gave evidence of a neuropathic habitus. To him it seemed that excessive indulgence in coffee, tea, alcohol, tobacco, etc., played a pathogenic rôle. Cazenave[13] believed that the cutaneous manifestations of neurodermatitis rather frequently alternate with various visceral manifestations, such as attacks of asthma, recurrent bronchitis, gastralgias, neuralgias or neuroses, etc. Fordyce,[14] in discussing the paper of Wise,[8] stated that in some cases foreign protein sensitization was the cause of the trouble.

Ehrmann,[11] after thirty years' study of the subject, concluded that various forms of autointoxication, especially the intestinal absorption of protein split products, disturbances of the pancreas, anacidity or hyperacidity of the gastric juice, etc., were the etiologic factors. Urbach,[4] Wise and Ramirez,[1] Sulzberger,[6] Biberstein,[5] reported series of cases where hypersensitiveness to various allergens was established. To Becker,[16] neurovascular instability accounts for the disease.

The patients studied in this report were not selected cases. They presented themselves in the dermatological clinic at Northwestern University Medical School, where a clinical diagnosis of diffuse neurodermatitis was made, and then they were transferred to the allergy clinic for immunological studies. Our results are identical with the findings of Sulzberger[6] et al., who reported nine cases of neurodermatitis and so excellently differentiated this type of dermatitis from the contact type. It is our aim in this paper to show that these patients give similar histories and findings of other allergic diseases as asthma and hay fever and that treatment based on allergic management gives results which have heretofore not been obtained by other types of treatment. These studies were undertaken in May, 1931.

CASE REPORTS

CASE 1.—Miss F. H., aged twenty years, student. Symptoms were pruritus plus lichenification with distribution on the antecubital fossae, neck, front and back, upper part of chest, face, eyelids and forehead, with loss of outer one-third of eyebrows. Duration was eight years. The patient suspected eggs as a causative factor.

Past History: Her grandfather had asthma. The eruption improves in summer and is worse in winter.

Complete skin tests were done. Cutaneous tests were all negative except a ++++ reaction to silk. Intradermal tests were all negative except silk ++++. Patch tests to silk and some of the commoner irritants were all negative. (Some clinicians who do not believe that protein sensitization bears any etiologic relationship in diffuse neurodermatitis state as arguments against these findings that local application of the allergen to the skin produces no eczematous reaction. This conclusion is erroneous because in neurodermatitis we are dealing not with an epithelial sensitization but with cutaneous sensitization.)

Treatment: On avoiding wearing silk since December 9, 1932, the pruritus cleared up, and at the present time the lichenification is gone and the skin is soft and smooth. Desensitization to silk was started. Locally only cold cream was used.

Case 2.—Miss A. E., aged thirteen and one-half years, gave a history of neurodermatitis for twelve and one-half years. Distribution was on the face, antecubital fossae, flexure surfaces of elbow, back of neck, back and chest. There was a loss of outer one-third of eyebrows. The skin was very dry with marked lichenification and intense itching. Cutaneous tests were all negative except silk ++++. Intradermal tests were all negative except silk ++++. Patch tests were negative.

Family History: An uncle has urticaria. Father has some form of eczema.

On avoiding wearing of silk the itching improved within two weeks. Desensitization had to be started with a 1:1,000,000 solution of silk protein because of the immense reactions obtained. At the present time the skin is completely cleared up and looks natural in every way. Desensitization is still being attempted as we have had to go very slowly because of her extreme sensitiveness. At one time owing to an error, a 1:1,000 dilution was given instead of a 1:100,000 and besides a rather severe local reaction, a large eczematous patch appeared on the forehead the next day and extreme itching of the body followed.

Case 3.—D. H., aged twenty, male. Neurodermatitis with the typical distribution was of twelve years' duration.

Family History: One brother has asthma; father has hay fever.

Cutaneous tests were all negative. Intradermal tests: wheat ++, cottonseed ++.

Passive transfer was done and was positive for wheat and cottonseed. Wheat and cottonseed were eliminated from the diet, the mattress was covered with rubberized sheeting, and the rash cleared up in two months and has remained clear up to date.

Case 4.—H. J., aged seventeen years, student. Onset of the eruption was fifteen years ago.

Family history was negative for allergic disease.

Cutaneous tests gave no reactions. Intradermal tests gave a ++++ to wheat (whole). Passive transfer showed reagins present to wheat.

On a wheat-free diet the eruption cleared up in four weeks.

Desensitization to wheat is being attempted by the injection method.

CASE 5.—Miss D. R., aged fourteen years. Neurodermatitis has been present since the patient was six months old. One year ago asthma began.

Family History: Father has hay fever.

Cutaneous tests gave +++ to egg (whole), +++ to oat, and ++ to cottonseed. Passive transfer showed reagins to egg (whole), oat and cottonseed. Egg and oat were eliminated from the diet, and also olive oil dressings, mustard, candy and all products containing cottonseed. The mattress was covered with an impervious material. The asthma cleared up promptly, and the skin improved within a period of four weeks.

CASE 6.—L. H., aged eighteen years, had had neurodermatitis since ten years of age.

No family history of allergy was obtained.

Cutaneous tests gave the following reactions: hog hair ++++, sheep wool ++, veal ++, bean +, shrimp +, glue +, salmon ++, pineapple +. Intradermal tests were: hog hair ++++, sheep wool ++, veal +++, house dust ++++. Passive transfer showed reagins to hog hair, sheep wool, veal and house dust.

All foods giving positive reactions were eliminated from the diet. Contact to wool was avoided. The patient lived in the vicinity of the stockyards; he was advised to change his residence, which he did, and the skin eruption gradually cleared up. We felt that the strong reactions to hog hair may have been an etiologic factor possibly by inhalation.

CASE 7.—Miss A. K., aged seventeen years, had neurodermatitis of five years' duration, and vasomotor rhinitis for the past year. She had had quartz lamp and roentgen therapy, thyroid medication and autohemotherapy for a considerable time without improvement.

Family History: One brother has hay fever.

Cutaneous tests were all negative. Intradermal tests showed a ++++ reaction to silk (1:1000). Passive transfer showed reagins to silk. Patch tests with silk and various cosmetics were negative.

On avoiding wearing silk and substituting cotton, the skin cleared up in a few weeks and desensitization was started. Because this patient also had a vasomotor rhinitis and silk was the only protein giving a reaction, a small amount of powdered silk protein was blown into one nostril and some inert talc was blown in the other nostril as a control. Within a few minutes marked itching was complained of fol-

lowed by a violent sneezing and watery discharge from the nostril in which the silk protein had been blown. There were also considerable local irritation and redness on that side. This experiment was suggested by Dr. Figley who saw this patient on his visit to Chicago. We, therefore, feel justified in concluding that at least some of these silk-sensitive patients become sensitized by inhalation of the silk protein and not by contact to the skin. The same experiment repeated on the other two silk patients gave the same results, and this may account for the observation that contact tests with silk give negative results in neurodermatitis.

Of the fourteen patients studied in our group we have outlined in detail the histories and results of tests in seven of them. The histories and findings in the remaining seven are so similar that we felt it would be time saving not to go into detail with each one separately.

SUMMARY AND CONCLUSIONS

1. Neurodermatitis is usually present in older children and young adults.

2. Nearly all patients give a positive allergic history.

3. Seven of these patients had other allergic manifestations.

4. In all cases the typical appearance and typical localizations were present, the most prominent being the scratched and lichenified lesions of the antecubital fossae.

5. The results of direct skin tests were positive in all except two patients, and in these, intradermal tests and passive transfer studies were positive.

6. Routine patch tests with the more common irritants; drugs, cosmetics and substances to which the patients were exposed in their environment were done with negative results, an observation which corroborates the findings of Sulzberger.

7. These patients all had complete laboratory tests including basal metabolism, blood chemistry including calcium and phosphorus, blood counts and urinalysis. There were no abnormal findings in any of these.

Sulzberger's observation that nearly all of his patients gave strong reactions to silk and had reagins to this substance has not coincided with our experience. One of us, S. J. T., reported 105 reactions to silk from a compilation of statistics on skin reactions to silk collected from the practices of fifty allergists over the country. Its etiologic significance was proved in only twenty-seven patients, twenty-two of whom had eczema and four of whom had urticaria. Among the cases in which it could not be demonstrated as an offending factor there were thirty-two of asthma.

We have routinely made several thousand tests with our silk protein in hay fever, asthma and various types of dermatitis with such a large

percentage of negative results that the only conclusion we can form is that a protein which gives so many reactions as reported by Sulzberger (silk protein) may be at fault and contains some histamine.

In conclusion we feel that this group of patients are best studied by the dermatologist and allergist, and it is suggested that the problem of sensitization in neurodermatitis be given more attention in the examination and study of the patient.

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SILK SENSITIVITY*

With Especial Reference to Its Rôle in Atopic Eczema

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During the course of the routine testing of several cases of allergic eczema we obtained very marked reactions to silk protein by the scratch method. This served to excite our interest in silk as related to eczematous dermatitis. Heretofore, the commonly accepted belief has been that silk causes eczematous dermatitis by its contact with the skin. However, as our work progressed, it was impressed upon us that skin contact alone could not account for the symptoms produced. The symptoms affected the respiratory tract as well as the skin, and furthermore, deliberately applying silk to the patient's skin did not cause any eczematous dermatitis. Our purpose then, in this communication, is to show that contrary to the accepted belief, silk is of more importance as an inhalant than as a contactant. In the few articles in the literature which have dealt with silk sensitization, and in the various textbooks on allergy, silk is mentioned almost solely as a contactant. In the light of our experience, we believe that it most often exerts its effect through inhalation, and will cite 5 case reports to substantiate this belief.

Silk sensitization, when it exists, is nearly always seen in connection with the skin condition variously known as "allergic eczema," "flexural eczema," "hay fever-eczema complex," or "disseminated neurodermatitis." We prefer the term "atopic eczema," because it is a true atopic manifestation, produced by atopens and for which reagins can be demonstrated. Atopic eczema is basically an immunologic problem and is one of the triad of proved manifestations of atopic hypersensitiveness, of which hay fever and asthma are a part. These three conditions may exist and usually are found present in the same patient. We especially prefer the term "atopic eczema" to disseminated neurodermatitis, because the latter implies and accentuates underlying emotional, neurocirculatory, and metabolic factors while completely ignoring the basic factor which is inherited constitutional hypersensitiveness or atopy.

Much confusion prevails regarding the subject of eczema because of terminology. European medical men give the name of eczema to what we call dermatitis venenata, or better, contact dermatitis, and use

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the term disseminated neurodermatitis for the condition we designate as allergic or atopic eczema. Also, many physicians fail to appreciate the basic differences between atopic eczema (disseminated neurodermatitis) and contact dermatitis (dermatitis venenata). Recently Sulzberger[1] has helped to clarify our understanding of these conditions by tabulating their salient differential features. He points out that in atopic eczema the family history is usually positive for allergic manifestations, the personal history is usually positive for other allergies, there is usually a history of infantile eczema, and the onset is usually before the age of twenty. The localization of the skin lesions is generalized, with marked predilection for face, neck, antecubital, and popliteal spaces. Vesiculation is practically always absent. Neurocirculatory instability is generally present. Direct skin tests, i.e., scratch and intradermal, give many positives with immediate wheal and flare. Indirect or passive transfer are usually positive to several substances, while patch or contact tests are almost universally negative. The excitants giving positive tests are usually foods and inhalants, as in asthma and hay fever—in other words, true atopens.

As contrasted with atopic eczema, Sulzberger states that in contact dermatitis the family history is usually negative, the personal history is usually negative for other allergies, and there is usually no history of infantile eczema. It appears at any age and localizes in any area, with predilection for exposed parts—face, eyelids, hands, and forearms. There is no particular favoring of flexures. Vesiculation is almost always present clinically and histologically in the acute stages, and it affects any type of skin. Neurocirculatory instability is not a feature of contact dermatitis. Direct and indirect tests are almost universally negative, while the patch test is positive, with eczematous reaction to one or more contact irritants during presence of eruption. The excitants giving positive tests are usually chemicals of known constitutional formulas and without protein. (Salts of metals, oils, etc.)

How is one to explain the rôle of an inhalant in the mechanism of a skin manifestation, be it eczema or urticaria? Our conception is as follows: The individual who is the subject of atopic manifestations, such as eczema, hay fever, or asthma, by inheritance has a constitutional make-up differing from the normal. He possesses numerous "shock-organs," such as the skin, gastrointestinal tract, nasal mucosa, and bronchi, any one or all of which are exquisitely sensitized to various atopens. His response to exposure to these atopens by ingestion, inhalation, or injection, depends on the size of the atopen dose and the degree of sensitiveness of the shock organs. Furthermore, such persons usually have marked neurocirculatory instability which causes their shock organs to respond readily to nonspecific stimuli. From

the above it can be reasoned that the skin as a shock organ can be affected by any atopen to which it is sensitized, whether ingestant, inhalant, or injectant.

Through the courtesy of Dr. E. W. France, director of the Textile School of the Pennsylvania Museum School of Industrial Art, we furnish the following information regarding silk. "The cocoon of the silkworm is made up of strands, better known as filaments, of an insoluble-in-water substance (fibroin) bound into a solid mass by a more soluble substance, known as sericin or 'silk glue.' The cocoons are placed in water sufficiently hot to soften the gum or glue. From four to six, as the case may be, of these filaments are grouped together, and the entire group is reeled off on a reel in such a manner as to make a combined thread, later known as the 'silk thread of commerce.'

"In most cases, at some stage of manufacture, this silk gum or glue is thoroughly removed, as far as it is practical to do so, from the fiber. In other cases, the silk gum is purposely left in the silk in the so-called 'souple' and 'ecru' (ecru—the name that is sometimes given to silk dyed in the gum) silk. In souple silks, about 10 to 15 per cent of the gum is left in the fiber, whereas in the ecru silk the percentage would range even higher. A relatively small amount of silk is processed in the last named manner.

"The silk 'gum' or 'glue' present in raw silk, amounts to about 24 to 26 per cent. Practically all silk is what is commonly known as 'thrown,' that is to say, the filaments are multiplied and twisted together to form a desired thread of a given weight. As a preliminary treatment to this so-called 'throwing process,' the raw silk or silk in the gum, as it is sometimes called, is put through a soaking bath in which olive oil soap and neat's-foot oil is commonly used. This softens the silk and to a certain degree weights it. The soap and oil, however, are removed at some later stage, before the silk leaves the plant for the consumer.

"Silk is almost invariably, and mainly to meet competitive prices, weighted. This process is usually carried out on silk that has had its gum or glue thoroughly removed. There are a number of different ways of weighting. A tin-phosphate-silicate process for blacks and colors; tannin, iron, logwood weighting for blacks is common. We also find, in the last few years, the use of lead salts along with the tin-phosphate-silicate process.

"After the weighting of silk comes the dyeing, usually with coal-tar dyes. Various sizing mixtures, containing gelatin, gums, acids, oils, etc., are used in finishing the silk in order to give it the proper handle. These latter remain in the finished silk until either a water or cleaning operation is given. Finishing ingredients to the amount of 8 to 10 per cent are often found present in silks in the consumers' hands."

Silk is one of the most powerful atopens known. It excites large skin reactions, and produces reagins which can be demonstrated with very high dilutions. It is prone to cause constitutional reactions from injection of weak dilutions. From the foregoing, it is apparently the gum or glue in the silkworm secretion which acts as the atopen. This is presumably high in protein content, as opposed to the contact dermatitis excitants which are nonprotein in nature. It is our belief that in those rare cases in which wearing silk may have caused a contact dermatitis, the skin eruption was effected by some substance with which the silk was weighted or dyed. Of its universal use in clothing, rugs, hangings, upholstery, shades, etc., nothing need be said. We do wish to call attention to the use of silk as a covering for the wires of lamp cords and other electric fixtures. This silk covering frays readily and in our opinion, contributes much of the air-borne silk particles of the modern household.

There is little or nothing in medical literature to substantiate the conception of silk as an excitant of contact dermatitis. On the other hand, all evidence points to its rôle as an atopen of the inhalant type. As the result of a questionnaire to determine the frequency of silk allergy, Taub[2] collected reports of 105 reactions to silk from the practices of forty-eight allergists. Its etiologic significance was proved in 22 cases of eczema, 4 of urticaria, and 1 of asthma. Its etiologic relationship was not proved in 38 cases of eczema, 17 of urticaria, 33 of rhinitis, and 32 of asthma. No mention is made of patch tests in these cases—the reactions to silk presumably being obtained by scratch or intradermal testing. Taub cites one of his own cases of eczema that reacted only to silk by cutaneous testing as giving a positive contact test to silk. He does not state with what material this contact test was made. In a study of 181 cases of atopic eczema Balyeat[3] obtained cutaneous reactions to silk in 9.9 per cent, but did not mention any positive patch tests to silk. Sulzberger[1] in a series of 9 thoroughly-studied cases of atopic eczema (disseminated neurodermatitis) says: "We first wish to call attention to the fact that nearly all the patients gave very strong reactions to silk and nearly all had reagins to this substance." He did not report any contact tests with silk in this series although many patch tests were done with practically negative results.

Clarke and Meyer[4] reported a case of asthma and mild chronic eczema in a woman twenty-one years old. She gave positive skin tests to house dust, rice, and flaxseed. She developed giant urticaria of arms, neck, and chest from wearing a silk waist, and had a severe constitutional reaction from an intradermal test with an extract made from pieces of this silk waist. No patch test was done in this case. Klauder[5] reports a case of dermatitis of the neck and arms in a woman

of sixty-one years from wearing black silk. He ascribed the dermatitis to the black silk and rubber shoulder straps. In this case the dye or the rubber may have been at fault.

As further evidence of our opinion that silk exerts its effect in atopic eczema as an inhalant rather than a contactant, we again refer to Sulzberger's paper. He says: "In all cases foods (as eggs, fish, wheat, and milk) were among the excitants eliciting positive response. The inhalants also elicited many positives, the strong reactions including those of orris, fowl epithelia, pollens, and silk."

He then cites one case which demonstrated that inhalants can cause skin exacerbations—a patient sensitive to pyrethrum, who, after inhaling insect spray, had to be hospitalized because of a severe generalized exacerbation of her eczema and asthma. Rattner and Pusey[6] recently reported a remarkable case of neurodermatitis (atopic eczema) in a young husband which proved to be due to perfume used by his wife. Certainly this, as an instance of inhalant sensitivity, compares closely with one of our patients whose eczema invariably flared up after inhaling gasoline fumes. Nowhere in the literature on atopic eczema is the fact stressed that inhalants play as great or perhaps greater rôle than ingestants. We wish to emphasize this fact. Three of our cases were pollen-sensitive, and had seasonal hay fever and asthma. Three of them were also sensitized to house dust and 2 of them to May fly. One of these patients was promptly relieved of her asthma and eczema by being placed in a dust-free hospital room, although the diet was not restricted.

CASE REPORTS

Case 1.—Miss R. H., aged sixteen years, was first seen in July, 1928. She had had eczema since the age of two, asthma since the age of three, and occasional attacks of hives. The eczema was typical of the atopic variety, involving the face, neck, upper chest and back, and antecubital spaces. The asthmatic attacks had become progressively more frequent until they occurred nightly. It is significant that severe exacerbations of the eczema and asthma coincided. There was no history of seasonal hay fever nor of any food intolerance. However, there was more or less sneezing and mucoid nasal discharge associated with the asthmatic attacks.

The family history showed that the maternal grandfather had asthma, the mother had asthma and hay fever, mother's brother had hay fever, one brother had asthma from rabbit hair, and one brother also had atopic eczema.

Complete skin testing by the scratch and intradermal methods gave strong reactions to silk and house dust. The history was then obtained that the patient had noticed that the wearing of a certain green silk dress had brought on asthma and stirred up the eczema. Intra-

dermal tests made with extracts from this silk dress and also other pieces of the patient's silk wearing apparel gave strongly positive reactions. Passive transfer with this patient's serum gave a strong positive reaction by scratch test to silk extract. Contact tests, using various pieces of the silk from which extracts had been made, and to which the patient reacted by intradermal tests, were all negative.

The treatment at first instituted, consisted of instructions to avoid wearing silk, together with the use of various ointments, lotions, and fractional x-ray dosage. The dermatitis responded promptly to this treatment, but the asthma was unaffected. Eventually the dermatitis recurred severely, and in November, 1929, silk desensitization was commenced. Injections were given by the patient's family physician over a period of seven months. At first, constitutional reactions were provoked by small amounts of a 1:10,000 dilution of silk extract. The maximum dosage reached was 0.5 c.c. of a 1:5000 dilution. Eventually, the dermatitis and asthma responded to these treatments, and there has been no recurrence of either for nearly three years, except an occasional mild bout of asthma following acute upper respiratory infections.

CASE 2.—Mr. D. E., aged twenty-four years, was first seen July, 1930. He had had eczema in childhood. At the age of five years, he developed asthma, which continued until the age of twelve. He had frequent year-round attacks. Three years earlier the asthma recurred in the fall and lasted only a few days.

The first outbreak of skin eruption began in December, 1925, while the patient was employed oiling machinery in a plate-glass factory. It affected the arms, popliteal spaces, neck, face, and scalp. The dermatitis persisted for some six months during which time the patient received treatment from one of us (H. J. P.). It was thought to be due to the constant soaking of the patient's clothes with lubricating oils while he was at work, and he was advised to find other work.

After quitting the job as oiler, the patient did brick-laying for a time, but again the dermatitis recurred. He later worked as a truck driver where his work exposed him to contact with oil and gasoline, during which time the dermatitis was very severe. Eventually, the patient gave up this work, and in the spring of 1930, while under the care of another dermatologist, he was hospitalized for some weeks. The dermatitis improved under hospital care, but peculiarly enough, he would have asthmatic attacks and skin flare-ups each time he was allowed a week-end visit at home.

As stated, the patient had eczema in childhood. He never had any hives or symptoms of food intolerance. The family history was negative for any allergic manifestations.

The initial physical examination in July, 1930, showed a well-developed man of twenty-four, with no apparent breathing difficulty. The chest was perfectly clear except for an occasional piping râle. There was present a pronounced dermatitis of the neck, forehead, upper chest, upper back, and the flexor surfaces of the arms and legs. This dermatitis was typical of so-called "disseminated neurodermatitis." The patient complained bitterly of itching, and there were many scratch marks and considerable lichenification as the result of the long-standing pruritis.

This man has been tested and retested many times by both scratch and intradermal technic. He gives huge reactions to silk, to some twelve foods, to ragweed pollen, May fly and mattress dust. He has definite exacerbations of the dermatitis from inhaling gasoline and naphtha, although scratch tests with these substances are negative. Reagins can be demonstrated to silk, wheat, egg, beans, pork, chocolate, ragweed, and mattress dust.

Contact tests were negative to timothy and ragweed pollen oils, to silk cocoon, powdered silkworm, raw silk filaments, and to "frison dust"—a dust consisting of particles of raw silk containing the pure gum. One of us (H. J. P.) made an exhaustive series of contact tests on this patient with crude oil and its various fractions as follows: crude oil; white furnace oil; medium, light, and heavy motor oil; red oil; gas oil; paraffin oil; heavy fuel oil; black furnace oil; kerosene and gasoline. These contact tests were all negative.

This man has been treated by every art at the hands of several dermatologists since 1925. In October, 1930, he had a severe constitutional reaction from the subcutaneous injection of 0.1 c.c. of 1:1000 silk extract. A little later, desensitization was attempted with a few doses of 1:20,000 solution of silk extract which only served to stir up the dermatitis and asthma. He again presented himself for allergic study in January, 1933, stating that he had avoided wearing silk as previously instructed but that he recently had a severe flare-up of his dermatitis shortly after his wife purchased two silk dresses. Retests in January, 1933, showed the usual tremendous reaction to scratch test with the Arlington powdered silk extract—the wheal measuring 40 mm. by 30 mm. Inadvertently, a little of the powdered extract blew into the patient's eye, causing a four-plus conjunctival reaction.

Treatment was started with 0.1 c.c. of 1:1,000,000 silk extract solution. There has been one reaction with 0.75 c.c. of the 1:1,000,000 solution, consisting of a flare-up of the atopic eczema and symptoms of hay fever lasting several days. At present the treatment doses are in the series of 1:100,000 strength. The atopic eczema is much improved, but subject to flare-ups from exposure to gasoline fumes or dietary indiscretions. Skin reactions to silk are considerably reduced

in size. There has been no asthma in recent years except during the May fly and ragweed seasons.

CASE 3.—Mrs. C. J. S., aged forty-one years, was first seen in November, 1931. She has had atopic eczema since the age of two years, which had been recurrent and usually worse in winter. At the age of eighteen she developed seasonal hay fever, lasting all summer and fall. Some ten years ago asthma began, and is now a year-round affair. There are free intervals between attacks. There was considerable cough accompanying attacks and rather profuse expectoration of greenish semi-purulent sputum after the attack subsided.

The patient had hives in childhood. Her mother formerly had asthma and now has epileptiform seizures. The patient's maternal aunt had "winter asthma," and one sister was sensitive to shellfish.

The patient is a small white woman, poorly nourished, having some asthma at the time of the initial examination. There was a diffuse, papulosquamous eruption over the following areas: cubital fossae, popliteal fossae, axillae, groins, under the breasts, inside of thighs, back of arms, on the hands, and over the face, neck, and scalp. There were many scratch marks and considerable lichenification. The picture was typical of so-called "disseminated neurodermatitis." Chest examination showed the usual findings of chronic asthma. On several occasions there was observed slight temperature and pulse rate elevation.

Extensive testing by the scratch and intradermal methods gave positive reactions to the grass and ragweed pollens, May flies, flaxseed, mattress dust, and a few foods. Contact tests using silk cocoon, raw silk, pollen oils, orris root, flaxseed, cottonseed, and other substances were all negative. In spite of dietary restrictions, dust elimination, etc., the patient was not benefited, and she discontinued her visits after a few weeks.

The patient again presented herself in January, 1933, with symptoms unchanged. She was sent to Toledo Hospital where retesting gave strong reactions to silk, flaxseed, mattress dust, pyrethrum, and grass and ragweed pollens. The silk sensitization was not discovered at the original testing, because we depended on a silkworm extract instead of the powdered raw silk. Passive sensitization tests done on two occasions gave large reactions to 1:1000 silk extract, and lesser reactions to grass and ragweed pollens and mattress dust. There was no passive transfer to reagins to pyrethrum or flaxseed. Contact test with silk was again negative. X-ray following lipiodol instillation of the bronchial tree showed saccular bronchiectasis at the base of the right lung. There was nothing noteworthy in the other laboratory examinations.

The patient remained in the hospital in a dust-free room some two weeks on an unrestricted diet. There was no asthma after her first

day there, and the skin cleared up markedly. After her return home, the patient had one short attack of asthma after putting away her silk clothing. Desensitization was started with 0.1 c.c. of 1:1,000,000 silk extract and is being continued. The dermatitis is well under control, and there is no longer the intolerable itching.

CASE 4.—Mrs. J. J. G., aged twenty-eight years, was first seen in April, 1933. She had her first attack of eczema at the age of six months. For at least ten years, she has had the typical distribution of atopic eczema. There is no definite seasonal hay fever or asthma, but she does occasionally have symptoms resembling hay fever, followed by chest-tightness and wheezing. She has hives at times. The patient's father had hay fever, and one cousin has hives.

The patient gives huge reactions to silk by the scratch test, the wheal measuring 55 mm. by 20 mm. There are also positive reactions to cottonwood and ragweed pollens, mattress dust, and twelve foods. Reagins can be demonstrated to silk, ragweed, mattress dust and five foods, of the cereal group. Contact tests were negative with raw silk and silk protein extract.

Following the scratch testing with silk extract there was a generalized flare-up of the skin eruption that lasted some ten days. This patient informed us that two years ago, she had generalized urticaria following the wearing of silk pajamas. The urticaria came on rather promptly and there were no other contributory incidents to account for it. Treatment by silk injection has not been attempted in this case, as complete avoidance of silk exposure has greatly benefited the atopic eczema.

CASE 5.—Miss M. H., aged thirteen years, has had eczema since the age of three months. At first it was of dry type affecting flexures of arms and legs chiefly. Of late years, eczema is typical of the atopic variety, and is generalized with much oozing and crusting. Asthma first began six years ago. This comes any time of the year and is accompanied by nasal symptoms. There is no history of definite seasonal hay fever. The father had hay fever and one of the patient's sisters, aged seven months, has eczema.

This girl gives a large reaction to silk by scratch test, and also reacts to egg and milk. Reagins can be demonstrated to silk, egg, and milk. Contact tests are negative to raw silk and silk protein extract. Avoidance of silk contact with elimination of egg and milk from the diet has given marked relief.

Attention is called to the fact that twelve other cases of atopic eczema that have been studied, failed to show any reaction to silk, although they reacted to many other substances including inhalants. This is cited to show that the silk reactions obtained in these five cases were specific, and not simply nonspecific reactions common to all cases of atopic eczema.

In cases of atopic eczema hypersensitive to silk, avoidance of exposure will occasionally suffice. However, because of its inhalant effects, it is often necessary to attempt hyposensitization by injection of silk protein extracts. These should be administered with care, beginning with very weak solutions because of the risk of constitutional reactions. Atopic eczema practically always means multiple sensitization of high degree. Consequently, other atopens must be properly dealt with, especially the inhalants. In all probability, a dust-free environment will be required in many cases, judging from the frequency of house- and bedding-dust sensitization in our cases. Finally, the allergist must work in conjunction with the dermatologist, in order that the patient may have the benefit of the best efforts of both.

SUMMARY

Five cases of atopic eczema are reported in which the major sensitivity was to silk and to which in each case, reagins could be demonstrated. Contact tests, using various preparations of silk were universally negative. All five patients had other manifestations of atopy involving the respiratory tract, and all but one reacted to other inhalants besides silk. From the evidence presented, we offer the opinion that in atopic eczema, silk exerts its effect as an inhalant rather than as a contactant.

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THE RAPID STANDARDIZATION OF PROTEIN EXTRACTS BY DETERMINING THEIR NITROGEN CONTENT*

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VARIOUS methods are used for standardizing the protein extracts employed in the diagnosis and treatment of allergic conditions. The simplest of these is the relationship between the weight of the antigen (pollen, orris root, etc.) and the volume of the solution in which it is dissolved, and it has recently been shown by Alexander[1] that this method is the one in most general use. Since it has been shown[2] that determination of the total nitrogen content of the solution probably gives a more accurate estimation of its potency, we have described below an application of a single micro-Kjeldahl method, for this standardization. In our opinion this method is sufficiently accurate for the purpose for which it is recommended, and is simple enough to be practicable in almost any laboratory. It certainly requires a much shorter period and less apparatus than do some of the methods now in use.

The method is based upon the technic for the determination of serum proteins recently described by Hubbard and Sly.[3]† This method utilizes the oxidation and nesslerization procedure described by Folin and Wu.[4] Precipitation of the Nessler's solution is prevented by the addition of small amounts of Rochelle salt. The exact procedure is as follows:

METHOD

Apparatus.—Digestion tube, 200 mm. by 24 mm., resistance glass; graduated at 35 and 50 ml.; watch glass 25 mm. diameter; micro-bunsen burner equipped with a chimney to protect the flame; four 1 mm. pipettes (Oswald).

Solutions.—1. Digestion Mixture: either one of the following may be used:

Sulphuric-copper sulphate mixture.[5] To 10 c.c. of 5 per cent copper sulphate solution add 100 c.c. of concentrated sulphuric acid. Carefully pour this mixture into 100 c.c. of distilled water, stirring constantly.

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*From the Helen Foster Allergy Clinic of the Children's Hospital of Buffalo, N. Y.
†Through the courtesy of the authors we have been using this method since May, 1932.

Phosphoric-sulphuric mixture.[5] To 50 c.c. of a 5 per cent copper sulphate solution add 300 c.c. of 85 per cent phosphoric acid and mix. Add 100 c.c. of concentrated sulphuric acid free from the least trace of ammonia, and mix. Keep well protected to prevent absorption on ammonia from the air. Dilute 1:1 with distilled water for use.

Either one of these mixtures may be used. The sulphuric-copper sulphate solution gives less precipitate and is probably a little better for general use. The phosphoric-sulphuric mixture is a more rapid digestion solution.

2. Nessler's solution.[5] Introduce into a 500 c.c. Florence flask 150 gm. potassium iodide and 110 gm. of iodine, add 100 c.c. of water and an excess of metallic mercury (140-150 gm.). Shake the flask continuously and vigorously for seven to fifteen minutes or until the dissolved iodine has nearly all disappeared. The solution becomes quite hot. When the red iodine solution has become visibly pale, though still red, cool in running water and continue the shaking until the reddish color of the iodine has been replaced by the greenish color of the double iodide. The whole operation does not usually take more than fifteen minutes. Decant the solution, washing the mercury and flask with liberal quantities of distilled water. Dilute solution and washings to 2 liters. If the cooling was begun in time, the resulting reagent is clear enough for immediate dilution with 10 per cent alkali and water, and the finished solution can be used at once for nesslerization. From this stock solution of potassium mercuric iodide prepare final Nessler's solution (containing about 55 gm. per 100 c.c.) which has been allowed to stand until the carbonate has settled, the clear solution being decanted and used. This solution may be purchased commercially if desired.

3. Ten per cent solution of Rochelle salts.

4. Standard Nitrogen Solution.* Dissolve and dilute 0.1414 gm. of the purest ammonium sulphate to 100 c.c. with distilled water (5 c.c. equals 1.5 mg. N). Dilute 50 c.c. of this stock solution to 150 c.c. with distilled water making a convenient standard for use (1 c.c. equals 0.1 mg. N).

PROCEDURE

The protein extract is diluted with distilled water so that 1 c.c. of the solution will equal approximately 0.1 mg. of nitrogen per c.c. (the strength of the standard). Reference to Table I shows the dilutions found convenient in some typical instances.

After the extract is properly diluted, mix the following in a digestion tube: 1 c.c. of extract, 1 c.c. of digestion mixture.

*This standard may be purchased from Hartman-Ledden Co., Philadelphia, Pa., 5 ml. containing 1 mg. nitrogen. Dilute this solution 50 ml. to 100 ml. then 1 ml. will contain 0.1 mg. nitrogen.

Heat slowly on the micro-bunsen burner until the water boils off and white fumes appear, and then cover the tube with a watch glass. Continue to heat until the solution first chars and then becomes clear white (a faint green tint may be present). Remove the flame and allow to cool for thirty seconds. Add slowly, drop by drop, about 5 c.c. of distilled water and then 1 c.c. of the 10 per cent Rochelle salts solution. Add distilled water up to the 35 c.c. mark. At this point the tubes may be corked and kept in a refrigerator for twenty-four hours, if desired.

TABLE I

SUBSTANCE	AMOUNT USED	AMOUNT OF EXTRACTING FLUID	APPROX. N PER C.C.	APPROX. DILUTION REQUIRED
Orris root	460 gm.	1900 c.c.	0.18 mg. per c.c.	1–1 (6)
Horse dander	*	*	3.3 mg. per c.c.	1–30
Cat hair	*	*	0.37 mg. per c.c.	1–3
Feathers	†	†	1.0 mg. per c.c.	1–10
Goat hair	†	†	0.1 mg. per c.c.	None
Rabbit hair	*	*	0.05 mg. per c.c.	None
Wool	†	†	0.1 mg. per c.c.	None
Mustard	1 lb.	1000 c.c.	6.4 mg. per c.c.	1–64 (6)
Cottonseed	40 gm.	1000 c.c.	2.3 mg. per c.c.	1–23 (6)
Flaxseed	40 gm.	1000 c.c.	0.23 mg. per c.c.	1–2
Glue	100 gm.	1000 c.c.	6.64 mg. per c.c.	1–66
Milk (casein free)	100 c.c.	100 c.c.	0.5 mg. per c.c.	1–5
Wheat	350 gm.	2600 c.c.	0.75 mg. per c.c.	1–7 (6)
Rice polish	225 gm.	2000 c.c.	0.3 mg. per c.c.	1–3 (6)
Rye	145 gm.	400 c.c.	1 mg. per c.c.	1–10 (6)
Oats	*	*	1.6 mg. per c.c.	1–16
Cornmeal	708 gm.	600 c.c.	0.45 mg. per c.c.	1–4 (6)
Meats	1 lb.	1000 c.c.	3.0 mg. per c.c.	1–30
Tea	*	*	1.0 mg. per c.c.	1–10
Chocolate	*	*	1.0 mg. per c.c.	1–10
Barley	*	*	1.0 mg. per c.c.	1–10
Peanut	*	*	5.0 mg. per c.c.	1–50
Pollens	3 gm.	100 c.c.	0.3 to 0.6 mg. per c.c.	1–5

*Because some substances vary to such an extent in the amount of nitrogen which may be extracted from them, it is sometimes advisable just to saturate the substance with the extracting fluid. These extracts were produced in this manner.

†These substances are extracted with difficulty so that after the first extraction is made, and extract removed, more of the substance to be extracted is placed into this same extract, thus increasing the atopen content of the final extract.

Reading: Standard—1 c.c. standard nitrogen solution; 1 c.c. digestion mixture; distilled water up to the 35 c.c. mark; 15 c.c. Nessler's solution. Mix by inverting the tube. To the extract add 15 c.c. of Nessler's solution. Read the extract against the standard in a colorimeter preferably by daylight.

Calculation.

$$\frac{\text{Colorimeter reading of Standard}}{\text{Colorimeter reading of Extract}} \times 0.1 \text{ (amount of nitrogen in standard)} \times \text{dilution} = \text{milligrams nitrogen per c.c. of extract.}$$

This method has been used to standardize extracts for the past year in this clinic. Previously to its use, extracts standardized by the

Kjeldahl method have been checked by this method and have been found to be accurate for the first two decimal places. Extracts standardized by this method have been compared by skin tests with those standardized by the Kjeldahl method and these also checked within reasonable accuracy.

CONCLUSION

A simple and accurate method of nitrogen determination applicable to protein extracts is presented. This method requires a small amount of apparatus and stock solutions, and is not time consuming.

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EPHEDRINE IN ALLERGIC MIGRAINE*

R. H. Kampmeier, M.D., New Orleans, La.

ALTHOUGH ephedrine has been used in the treatment of certain allergic manifestations since its introduction some years ago, a search of the literature does not reveal any report of its use in the relief of symptoms in migraine on an allergic basis.

I have had an opportunity to note the effect of the drug in migraine under close personal observation. The patient in question, a young adult, has suffered from migraine for about six years. By a check upon the diet it was determined that certain articles of food would provoke an attack of hemicrania associated with gastric symptoms, of which eructations of gas are the main one. About three years ago ephedrine was suggested in an experimental way, for treatment of the attacks. It was found that if three-eighths of a grain of the drug were used at the onset of symptoms, the attacks was aborted in about 75 per cent of instances. If the attack was allowed to become established, relief apparently occurred in a smaller percentage. In case the attack was aborted, the gastric symptoms disappeared and a dull headache persisted rather than the pain of the migrainous attack.

At first ephedrine sulphate was used by itself, but in the last two years a capsule containing ephedrine sulphate three-eighths of a grain, and amytal three-fourths of a grain (Eli Lilly & Co.) has been used. The inclusion of the second drug apparently decreases the unpleasant symptoms of palpitation and nervousness which result from the ingestion of ephedrine in this particular patient. I have occasionally used this mode of treatment in other patients in isolated attacks. However, it has not been possible to carry on prolonged observations as in the one case.

It seems not unreasonable to believe that the drug may have a beneficial effect, especially as an aid in aborting a migrainous attack. Those who have taken histories in patients suffering from migraine h[illegible]t infrequently obtained a story suggesting gastric retention due to [illegible] rospasm. The patient may give a history of having vomited [illegible]n foods practically unchanged, twelve to twenty-four hours after ha[illegible] eaten them. For example, one patient, a physician's wife and a [illegible] intelligent woman, who had suffered from severe migrainous atta[illegible] weekly for about twenty years, volunteered the information th[illegible] whenever she ate orange an attack occurred, and that this food wou[illegible] be returned in the vomitus twenty-four hours later. Upon skin testing

*From the Louisiana State University Medical Center, Department of Medicine.

I found her to be very sensitive to orange as well as to other substances. (Incidentally, after elimination of the foods to which she was sensitive she had only one attack of migraine in sixteen months.) Similar histories of delayed vomiting of food have been obtained at various times.

Fray[1] in a roentgenologic study of the effect of ephedrine sulphate upon gastric motility found that the drug commonly produces a diminution of peristalsis and of tone in the human stomach free from intrinsic disease. The drug was found to relax pylorospasm of functional origin more often than that associated with local disease. However, even here it was variable.

The action of ephedrine in migraine may be difficult to explain. Vasomotor effect to relieve possible localized cerebral edema, which is Balyeat's[2] conception of migraine, may be one explanation. But the vasomotor effect might well be associated with decreased absorption of the offending allergin. This explanation would seem more reasonable in light of the data of the accompanying case. The effect of the drug is greatest in aborting an oncoming attack. This conception of beneficial effect on the gastrointestinal tract is strengthened by the marked relief of the gastric symptoms, namely, the eructations of air constantly swallowed to relieve the gastric distress. Such relief evidently results from abolition of pylorospasm with attendant emptying of the stomach which may lead to decreased absorption of substances to which the patient is sensitive.

Whatever the mechanism may be of the action of ephedrine, because of its unquestioned beneficial effect in a closely supervised intelligent patient, the recording of this fact seems worth while. Again emphasis is placed on its use at the onset of symptoms in order to abort the attack. It is hoped that those whose practice offers the properly selected cases will give a more extensive trial to this drug.

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Society Proceedings

THE ASSOCIATION FOR THE STUDY OF ALLERGY

ELEVENTH ANNUAL MEETING, MILWAUKEE, WIS.,
JUNE 12 AND 13, 1933

Angina Pectoris Syndrome Activated by Ragweed Sensitivity in a Patient With Coronary Vessel Sclerosis. CHARLES SHOOKHOFF, AND D. LEONARD LIEBERMAN, Brooklyn, N. Y. (For original article, see page 513, September issue.)

Hypersensitiveness to Acetylsalicylic Acid Expressed by an Angina Pectoris Syndrome, With and Without Urticaria. CHARLES SHOOKHOFF, AND D. LEONARD LIEBERMAN, Brooklyn, N. Y. (For original article, see page 506, September issue.)

DISCUSSION

DR. ALBERT H. ROWE, Oakland, Calif.—I have long thought that there is no reason why the smooth muscle in the cardiovascular system and the heart itself should not be the seat of allergic reactions. Most of the other smooth muscles in the body have been shown to be more or less subject to these reactions, and the muscle of the heart and the smooth muscle of the blood vessels should theoretically not be exempt from this effect.

In the observations that I have made during the last ten or twelve years I have certainly felt that allergy has been an exciting cause in certain cases for cardiac disturbances and irregularities. On two or three occasions I have apparently observed similar phenomena that Dr. Shookhoff has reported in the cases today.

Recently I have had an opportunity to observe a case very similar to the first case he described this morning. This was a woman about seventy years old who had been confined to her bed more or less for three or four years because of anginal symptoms. The physician called me in consultation because of the fact that recently during the grass season her symptoms were greatly exaggerated. Throughout the year this woman has been in bed more or less, and I believe she has undoubtedly very definite arteriosclerotic changes in her blood vessels and changes in her electrocardiogram. Around San Francisco Bay, we have grass pollen in the air throughout the year especially in May and June and her symptoms were very much exaggerated during these recent months.

I tested her and found her skin negative, but due to her definite seasonal history of moderate asthma and exaggeration of these symptoms at this time we put a pollen filter in her room and began to desensitize her with pollen. After the first two or three days she has been completely free from all anginal symptoms. The physician has had an opportunity to observe this woman for a great many years, and he is very sure this result has accrued. I believe you would have to interpret this pollen effect as an exciting cause rather than as a primary cause of her angina.

DR. ROBERT L. BENSON, Portland, Ore.—The case I wish to refer to briefly is in line with one to which Dr. Cohen called attention a couple of years ago in a very timely way, and involves the danger of morphine in asthma practice.

The case that I refer to was a severe asthmatic who was progressing very well. She had told me repeatedly she was afraid of aspirin, yet in another city fifty miles from Portland she once called for an aspirin tablet. Her husband, under protest, gave it to her. He returned two or three minutes later and found her dead.

I merely report this as what I believe to be an acute death in asthma from aspirin.

DR. A. H. W. CAULFEILD.—Before I ask Dr. Shookhoff to reply, I should like to put a question myself. Recently I had a case very similar to the first one mentioned except that the cardiac disease had preceded any allergic manifestations for some years. At postmortem a rather unusual finding presented.

There was marked enlargement of the heart and the left vagus, and when dissected out was about twice the size of the right vagus. Also, at the same time there were small glands lying between the pleura, which was adherent. If one looked at it in one way, one might think some pressure was brought to bear on one of the vagi or even the sympathetic fibers.

I should like to ask Dr. Shookhoff whether he had a postmortem examination on his cases.

DR. SHOOKHOFF.—Our first patient is alive. We do not believe allergic hypersensitivity is the cause of cardiovascular pathology. We do not think that allergic states cause gross permanent pathologic changes. The point we mean to make is that there are patients sensitive to various substances in whom anginal syndromes are an expression of that hypersensitivity, and we believe that these cardiac manifestations may be relieved to some degree by methods directed toward the alleviation of the atopic sensitivity. These patients all have evidence of cardiovascular degenerative disease. We feel "that the cardiovascular pathology, which has no etiologic relationship to the hypersensitivity, may cause the cardiovascular system to become the shock organ in these hypersensitive individuals. Thus cardiovascular symptomatology may become an expression of hypersensitivity."

There is one other point we should like to make in these cases. In the pollen case the attacks were of short duration, were not accompanied by signs of cardiac collapse or insufficiency, and the blood pressure was always increased. They seemed to have a spastic character. In the acetyl salicylic acid group the blood pressure dropped considerably, and signs and symptoms of cardiovascular collapse were present—the usual signs and symptoms, however, of an accompanying myomalacia, temperature, sedimentation time, leucocytosis, etc., were absent. It appears that some temporary cardiac involvement must have taken place. What the nature of this involvement is, we cannot say.

In reply to Dr. Caulfeild, we would again repeat, we do not believe that allergy or hypersensitivity is the cause of the cardiovascular degenerative disease. What part the vagus played in the causation of

the symptomatology in these cases we cannot say. An imbalance of the extracardiac nervous mechanism may have played some part in the causation of the symptoms in the pollen case; we are not so sure about the acetyl salicylic acid cases. The vagal tone is markedly disturbed in myocardial disease as well as in allergy, and a hyperirritable vagus is considered one of the signs of myocardial involvement, rather than one of its causes.

Intradermal Pollen Therapy During the Attack. E. W. Phillips, Phoenix, Ariz. (For original article, see page 29.)

DISCUSSION

Dr. I. S. Kahn, San Antonio, Texas.—In not more generally adopting the intradermal treatment of acute hay fever and asthma I feel our specialty is overlooking one of the greatest advances yet made in seasonal pollen therapy. Dr. Phillips mentions the disadvantages of pain and scarring. Both can be kept at a minimum by using dosages not over 0.04 c.c., and in women these treatments can as easily be given in the thigh.

Desensitization is often very rapid, and within a few days or two weeks high concentration protecting dilutions are tolerated, where at the start extremely weak dilutions were all that could be employed. The clinical improvement so paralleling is consistently almost extraordinary. Injection areas must be changed with each dose to avoid the possibility of false reaction absences due to skin reactivity exhaustion. By giving every few days a distinct good typical four-plus wheal, clinical protection so derived can easily be continued throughout the season. Like Dr. Phillips, I have numbers of patients who prefer this to the usual preseasonal treatment, securing consistent prompt relief after their hay fever season starts.

Dr. Leon Unger, Chicago.—I have tried the intradermal method of treatment, but not with such brilliant results as Dr. Phillips reports. I am glad to hear somebody report he can get 91 per cent of good results with intradermal therapy.

I have tried both the intradermal method and the subcutaneous method in coseasonal injections. I have not seen any particular difference in the results of the two conditions. I do not know why the intradermal method should give better results than the subcutaneous method. I cannot see any real logic in such difference of results.

Dr. Phillips' statement that he had some scarring from intradermal injections of his glycerin extracts leads me to discuss the dextrose solution with which we have been working. The paper on the use of dextrose-cresol solutions of ragweed pollen was recently published in the Journal of Allergy. The reasons we worked with this dextrose solution were the following: We wanted some solution which is painless; we wanted a solution which one can inject intradermally; and we wanted a solution which one can draw through fine needles. We found that dextrose solution was such a solution. Dr. Moore was the author of the solution, and I did most of the clinical work.

We found 5 per cent dextrose solution would give a very, very good extract; that it was practically painless; certainly it caused much less pain than any glycerin solution we had previously used.

We found one could inject it intradermally without causing much pain and without causing the marked swelling which is characteristic of glycerin solutions. We found it drew up in the needles easily.

Incidentally, some of you will recall that a questionnaire was sent around to the different men to whom a sample supply of this dextrose solution was mailed. In this questionnaire we asked them about the pain and about the worth of this particular solution. All those who replied said the pain was practically none. Some of them said they had very good results with the treatment.

I want at this time to report a little further work with this dextrose solution. We have continued using it and have put our patients on it. We have used it intradermally for about a year, and we thus have become better acquainted with it. We find that it has fully lived up to our expectations, in that one can draw it through fine needles, that it is painless, and that one can inject it intradermally without causing great discomfort. Incidentally, we find that the potency of the dextrose solutions is equal to that of the glycerin extracts.

We have had some severe reactions with the dextrose solutions, just as we had in our previous use of glycerin extracts. I think Dr. Phillips, in his future intradermal therapy, would do well to try some of the dextrose solutions. He will find them stable. We kept solutions in an incubator for a period of over a year and found positive skin tests thereafter.

I want to recommend the dextrose extracts of ragweed and grass pollen, not only for the intradermal method of treatment and intradermal testing of hay fever cases, but also for the usual subcutaneous treatments.

Dr. Robert L. Benson.—I have used the intracutaneous method considerably in coseasonal work, and the local reaction I find can be overcome very successfully by using neither glycerin solution nor glucose solution, but simply the Coca solution, or saline, it does not matter, but making the solutions up frequently. We follow the practice of making them up once a week during the season.

With these things in mind, I have no hesitation whatever in taking a case in season and giving as high as three injections daily. There is no reason why we should not give three similar sized injections today, with the probability tomorrow that we can start as our first dose a summation of the doses of the preceding day.

Then there is one other point. I wish to mention that if we keep our patients off fruits during this course, probably the results of our coseasonal work in particular can be brought up much more nearly to 100 per cent of successful results. Fruits, regardless of the specificity of the individual for any particular fruit, have in my experience some sort of a disturbing effect, whether due to the alkalinization or what it is I do not know, but I find the individual will stand less pollen if he is on a fruit diet than if he is on a diet which entirely precludes fruit.

Dr. B. Z. Rappaport, Chicago.—Regarding Dr. Unger's remark about the absence of any basis for intradermal therapy in preference to subcutaneous therapy, I recall vaguely a piece of work by Franz Müller, in which insulin was used intradermally and subcutaneously for the raising of blood sugar. Comparing the two methods (I do not think

this is the primary object of the problem; this was an incidental observation), there was a much more prolonged effect from the insulin used intradermally than from that used subcutaneously. There is a relation between the skin and the parasympathetic nervous system. There is a more prolonged effect by the use of intradermal technic than by the use of the subcutaneous. I am not speaking of pollen therapy per se. I am speaking of the effect on the sympathetic and parasympathetic nervous system, if I may be so vague, by intradermal stimulation.

Even with stimulation of the skin in Besredka's work with and without scarifications, the effect is much more marked than that which can be produced by subcutaneous injections. I think the effect of intradermal therapy is definitely on a different basis from that of subcutaneous injections. Whether it is more favorable or not, I do not know. With intradermal therapy the results produced depend not so much on the dose you give, but on the stimulation of the autonomic system, which has considerable to do with immunization.

Dr. R. W. Lamson.—That relief may be obtained by intradermal pollen therapy is beyond question. Although you may not employ this method, I am sure you have had the following experience. A patient has symptoms at the time he is given the tests. Definite positive reactions are obtained by the intradermal, or even the scratch method. At the next visit the patient asks, "Is it possible that what you did the other day gave me relief?" He noted improvement shortly after the skin tests.

I still wonder whether or not intradermal treatment has any special efficacy over the subcutaneous method, and whether, as Dr. Benson has intimated, smaller doses may be employed with equal success. I have always understood that the absorption of a drug or other substance was slower from an intracutaneous than from a subcutaneous site, and is still more rapid when injected intramuscularly. As a corollary, one would expect the intracutaneous route to require a larger dose to produce a result identical with that following intramuscular or subcutaneous injection.

I have asked physiologists and anatomists if there is to their knowledge, any reason why the skin should be considered a tissue quite separate from the rest of the body; should it differ from the subcutaneous tissue in its ability to produce immunity or hyposensitivity, especially of a rather distant tissue such as the respiratory tract? I have thus far received no support for such an assumption.

Besredka believes in specific skin susceptibility, and hence immunity, as distinguished from the response in other tissues. He cites the familiar experiment of producing a fatal infection with anthrax bacilli by intraperitoneal injection into a guinea pig. He contends that many lethal doses may be given without damage to the animal if one protects the skin from contamination during the introduction or withdrawal of the needle. Zinsser and his associates repeated these experiments and were unable to substantiate Besredka's claims.

The latter does not limit his concepts of local tissue immunity to the skin. He believes that susceptibility to typhoid is a function of the tissues of the gastrointestinal tract. It is most logical, therefore, to attempt to immunize it rather than the subcutaneous tissues of the up-

per arm. He has employed oral vaccines for this purpose. Whether these are going to be of prophylactic value remains to be shown.

I should like to call attention to two points brought out by Dr. Kahn. Before so doing I should state that I belong to the school that believes in the specificity of therapy, yet I am not convinced that heterologous pollen therapy may not ultimately be firmly established. Dr. Kahn treated certain of his patients with timothy pollen. I wonder how many realize that there is no timothy grass within a thousand miles of his community.

The second point should be particularly interesting to those who believe that skin reactions are not modified by treatment. In spite of the absence of timothy from the environment of the patient and the fact that reactions to it were somewhat weaker than to grasses of that region, a condition of skin hyposensitivity to grasses followed after ten days of intracutaneous treatment. Clinical results also seemed quite satisfactory. These problems justify more than passing attention.

I occasionally use Dr. Phillips' method and believe that it may have a margin of safety over the subcutaneous route of injection, especially on the very sensitive patient. If it is impossible to keep the patient under observation for an adequate period after treatment, the intracutaneous method may be the one of choice. Possibly the same protection may be obtained if epinephrine is included with the material to be given subcutaneously. Delayed absorption is probably the factor in each method.

The data at hand are not sufficient to support the assumption that the skin, as contrasted to the subcutaneous tissue, has some peculiar physiologic or immunologic property.

Dr. George L. Waldbott.—Dr. Phillips entitled his paper, "Intradermal Pollen Therapy," and not coseasonal treatment. It would have been interesting to see how intradermal therapy compares with subcutaneous and intramuscular therapy. I believe most of us have had experiences similar to that of Dr. Phillips with coseasonal treatment. It is my belief, however, that the effect of this treatment depends upon the production of a local edema and that it matters little whether this edema is located between the two layers of the skin or in the musculature.

Dr. M. Murray Peshkin, New York City.—The more one listens to papers and discussions dealing with the treatment of hay fever, the more one becomes convinced that successful pollen therapy depends upon the experience and individualization that each worker puts behind each dose rather than upon the method of treatment used. For these reasons many statements on the subject seem conflicting and contradictory. It is not surprising therefore that the general practitioner frequently is confused when the question arises as to the best method of treatment to employ.

Last year Dr. Vaughan reported on a group of patients with hay fever in whom only the coseasonal subcutaneous method of treatment was employed. The first dose was empirically set at 0.10 c.c. of 1:5,000 extract of pollen. The patients reported quick relief from symptoms. Dr. Vaughan predicted that this form of treatment, as far as he was concerned, may supplant the tedious preseasonal method. The results, before they can be accepted, must be substantiated by other workers.

Dr. Phillips, after seven years of additional study with the treatment of hay fever by the intradermal method (which is essentially a coseasonal plan of treament) is convinced of the superior efficacy of this type over all other forms of treatment. These results, before they can be accepted, must also be substantiated by other workers.

Patients with hay fever applying for treatment during the pollen season usually show large local reactions (subcutaneous method) to such dosage, which, when given preseasonally, will frequently cause no local reactions whatsoever. The immediate and delayed reactions following the skin tests (scratch and intradermal technics) are usually also more marked during than out of the pollen season. Following the diagnostic skin tests during pollination, patients frequently report improvement in their symptoms, indicating that successful coseasonal treatment of hay fever, however administered, is essentially a method of treatment involving small dosage. When the same patient the following year is submitted to the preseasonal plan of treatment he will be found to require higher dosage for protection, regardless of the type of the previous plan of coseasonal treatment employed.

Since only small dosage of pollen extract can induce beneficial results with the coseasonal treatment of hay fever, the intradermal method of treatment may take precedence over the subcutaneous and scratch methods. The latter modes of treatment require perhaps from ten to one hundred times more pollen for the same amount of relief from hay fever than the intradermal method.

It is important and of interest to learn from Dr. Kahn that patients with pollen asthma and hay fever refractory to a 1:50 or 1:20 pollen extract by intradermal test can also be relieved of symptoms from coseasonal intradermal treatment.

However, in the final analysis, one could make the safe prediction that the coseasonal treatment can only serve as an adjuvant and will not supplant preseasonal treatment of pollinosis.

Dr. Siegfried Maurer, Chicago, Ill.—I should like to say a word about anatomic studies of the intradermal injection. Histologic studies of the intradermal injection have been made by Dr. Paul Cannon of the University of Chicago. Locally immunized and normal rabbits and guinea pigs were used in the experiment. In the normal animal living staphylococci rapidly diffused from the point of intradermal injection, while when the living bacteria were injected intradermally into skin which had been previously locally immunized by the intradermal injection of killed staphylococcus, the living bacteria were prevented from diffusing from the site of intradermal injection. In both these animals the living staphylococci were found soon after injection in the heart's blood. From these experiments it would appear that even intradermal injection is to some degree an intracapillary injection.

Opie has demonstrated that when normal rabbits are injected intradermally with foreign protein, such as crystalline egg albumen, or horse serum, much of the material is quickly demonstrated in the blood stream; with repeated injection of the antigen the quantity of foreign protein that enters the blood stream diminishes, and finally with advanced immunization none enters unless massive doses have been employed. This fact would make it appear that at least part of the intradermal injection of pollen antigen is really intravenous.

DR. CHARLES H. EYERMANN.—I just want to inject a query. This method is so uniformly successful, I think 84 per cent?

DR. PHILLIPS.—Ninety-one and six-tenths per cent.

DR. EYERMANN.—The percentage of success is at least comparable to, if not better than, the old orthodox preseasonal treatment. Since this success is obtained by a fewer number of injections, or at least by a fewer number of days treated, has it superseded in Dr. Phillips' experience the orthodox preseasonal treatment, and if it has not, why hasn't it?

DR. GEORGE PINESS, Los Angeles, Calif.—The report of Dr. Phillips getting 91.6 per cent of relief is an arbitrary measure due to the fact that those of us who have made reports in the past, on the relief obtained from pollen desensitization, have divided it into four groups: those who obtained complete relief, practically complete, partial, and no relief.

If you take the figures of the men who reported series of cases, such as Vanderveer, Cook, and myself, and I think Rackemann and Caulfeild reported some, and figure up the number of cases that obtained relief according to the definition expounded by Dr. Phillips of what relief consisted of, then the orthodox method gives equally as good results as the method suggested by Dr. Phillips. Incidentally, too, as I understand it, it is a method of coseasonal treatment.

On the question that comes up as to the nature of solution for a diluting fluid or extracting fluid that is used in the preparation of these antigens, glycerin solutions are much more satisfactory. They are no more painful if the solution is not more than 50 per cent glycerin, they will keep longer, and are more stable. I am not in accord with the opinion of Dr. Peshkin, as I will prove this afternoon, that these solutions only last from six weeks to six months.

It is true that other solutions that have been used, such as Walker's original solution of 15 per cent alcohol and saline, will turn sour in a very few weeks whether in the ice box or exposed to the air, and that the solution prepared by Coca is not a good solution because it does precipitate the proteins and solid matter that are contained in the solution, and that it is not stable and will not continue to be good over a period of several months. I have tried to bring that out in the paper which I am to present this afternoon.

Getting back to the discussion of Dr. Phillips' paper, in our experience we find, and I think Lamson has seen this in our office, that by the scratch testing we were able to get equally good results as those we obtained by intradermal treatment, and also that some of these patients think the scratch test is a treatment and have accepted it as such because they get relief.

I think when we analyze the whole situation, we find the preseasonal treatment as given in the orthodox way, but with caution, most satisfactory. We must remember, however, that there is no stereotyped dosage, that you have to measure your dosage according to the individual, cutting down or repeating as often as is necessary to prevent reactions, which do two things: They give constitutional symptoms, and drive patients away from your office.

DR. WARREN T. VAUGHAN, Richmond, Va.—Answering Dr. Eyermann's question, I should not be at all surprised, in the near future, to see coseasonal treatment supplant preseasonal treatment. We get such good results with coseasonal treatment that it is hard thereafter to get the patient to come in for preseasonal or perennial treatment.

We usually use subcutaneous medication. We do not find it necessary to run the dose up to 1:50, as Dr. Kahn does with intracutaneous treatment. We keep the dose way down. When we do use intracutaneous treatment, we never use glycerin because it is chemically irritating.

If we have our stronger solutions made up in glycerol saline, we make our dilutions in one of the menstruums which do not contain glycerin, and in that way I think we avoid any tendency to scarring.

We do use Dr. Phillips' method of cutaneous coseasonal desensitization, particularly where there is a short period of symptoms as in tree pollinosis. Then, we can usually get very satisfactory results just from daily scratch desensitization.

DR. HARRY L. HUBER, Chicago, Ill.—May not the close embryologic relationship of the dermis and mucosa give a basis for the explanation of the beneficial results obtained by intradermal treatments? The mucous membrane is only infolded skin.

Following the first publication of Dr. Phillips' observations on intradermal treatment I began to use the scratch test treatment method in all pregnant patients and have found it a very satisfactory method. This is a modified intradermal treatment that takes more time but is safer.

DR. PHILLIPS.—A good many of these questions would have been answered if I had been as quick of speech as Floyd Gibbons, and had read the paper as it was written. It was too long for the allotted time.

Taking some of the points which Dr. Kahn and Dr. Peshkin brought out, I try to change the site of injection every time because, as noted in the original paper in 1926, the amount of relief which comes is dependent not only upon the actual quantity of pollen extract injected, but upon the extent and vigor of the local reaction. I have always felt that something produced in that local reaction in the skin, and released from there—perhaps some substance allied to histaminase—helps the allergic patient to deal with pollen in a normal way. So I try to get big local reactions and the patients demand them after they have once experienced the relief which follows. I sometimes give two doses in a day; usually only one.

I have not yet tried the dextrose solutions. I shall next year. I am positive about this finding: glycerin does scar some skins, perhaps 6 or 8 per cent, and equivalent extracts in Coca's fluid do not scar those very same people in the corresponding dose.

Dr. Benson mentioned fruits. I occasionally instruct hay fever patients to avoid cantaloupes, cucumbers and strawberries in the spring. Sometimes indulgence in those seasonal delicacies spoils a good result.

In my original paper on this subject, I reported relief from scratch tests. When I started using Bermuda grass pollen, none could be bought; so I applied raw pollen to progressively enlarged scratches. I did that until I could collect enough Bermuda grass pollen to make a good extract.

Replying to Dr. Waldbott's question as to controls: I have none. These were all private patients and I had to do the best I could for them. I think that by this method I get better results than I ever got with preseasonal treatment. I know that I have relieved by this method many patients who were not relieved by preseasonal treatment. When giving preseasonal treatment I find it is best to continue the dosage well into the pollen season, as Cooke long ago advised.

Dr. Peshkin will remember that I did not say the intradermal coseasonal method is the best way of treating hay fever. I said that it is a good method. That is all I can say. One cannot make a comparison on the basis of the varying reports available.

As to what happens to the intensity of the positive skin reaction during the treatment, in the paper it will appear that these patients divide themselves roughly into two groups. With most, the skin reaction is not much altered by the time they are relieved, but there is a minority who require a much larger number of doses, so that one comes up to a fair-sized dose, a third or a fourth of what one would use in preseasonal treatment. In such patients the skin reaction is definitely lessened by the time the course is completed.

In the first paper on this subject, I gave credit to Dr. Vaughan for the work which he had published in, I think, 1912, or somewhere back there.

DR. VAUGHAN.—In 1922.

DR. PHILLIPS.—I was only ten years out. He was at that time treating hay fever by small daily doses subcutaneously.

DR. C. N. HENSEL.—Do you mean us to understand that seven to ten days of intradermal treatment will relieve the patient throughout the whole of the rest of the hay fever season? Or does that intradermal course have to be repeated again from time to time?

DR. PHILLIPS.—A series of daily doses until relief occurs, with injections at longer intervals thereafter up to a dose at least twice that which effected relief, usually protects for the remainder of the season —even the prolonged pollen season of Arizona. But quite a few patients stop treatment as soon as they get relief, and some of these, if their dosage has been inadequate, have a recurrence of symptoms. In such cases the treatment has to be resumed.

The Preservation of Pollen Extracts by Drying and the Preparation of Concentrated Pollen Solutions. B. Z. RAPPAPORT, Chicago, Ill. (For original article, see page 13.)

DISCUSSION

DR. GEORGE PINESS.—I want to ask Dr. Rappaport just one question. Was the nitrogen determination total nitrogen, or was it protein nitrogen?

DR. RAPPAPORT.—Total nitrogen.

DR. PINESS.—If that was total nitrogen, your findings give no real positive proof as to the value of the concentrations you make.

Cook recently reported that in his study of pollens particularly (and we were discussing pollens this morning) he finds that the protein nitrogen content of the pollens varies, that they are not constant

in various genera or classes of pollen. I think, if I remember that paper right, that he showed the ragweed was the one that had the largest amount of protein nitrogen, and that the difference between the protein nitrogen and the total nitrogen sometimes was one to one, or one to two, or even as high as one to four.

On the whole, I see no advantage in going through this procedure, if what those of us who have done this work over a long period of time have found is true, which is quite in accord with his opinion, that concentrated solutions are stable. If we believe this is true, then I see no sense of going to this extreme of making a jelly and redissolving it each time you need it. I think I can prove to you the stability of protein and protein solutions, which I hope to do later in the day.

DR. RAPPAPORT.—In answer to Dr. Piness' question, I want him to see the diffeernce in the appearance of the concentrated and dilute solutions. I think the gross appearance of the two solutions is sufficiently different to answer his question.

If the total nitrogen is raised to four and one-half times the original nitrogen, the protein nitrogen is raised in proportion if almost all of the material is in solution. The method permits one to prepare a solution four and one-half times as concentrated as the solution ordinarily used.

The advantage of having it in a powder is that you have material which can be put away, which can be re-prepared in smaller quantities as it is needed, instead of preparing a batch of material to use for six months.

We do know one thing about proteins, and that is they will not deteriorate when they are kept dry. Otherwise, I do not know of any protein solution that will remain completely stable. At least, biochemists do not know of any stable protein solution. It deteriorates with age very rapidly. That is why I prefer to have powder available that can be prepared in the matter of an hour into a fresh solution.

Allergy a Constant Factor in the Etiology of So-Called Mucous Nasal Polyps. RICHARD A. KERN AND HARRY P. SCHENCK, Philadelphia, Pa. (For original article, see page 485, September issue.)

DISCUSSION

DR. BERNHARD STEINBERG, Toledo.—I think Dr. Hansel will bear out in the discussion which he will probably join that there is a definite hisopathology associated with allergic sinusitis. I had the opportunity in the past several months to confirm Dr. Hansel's work. These confirmations were presented a few days ago at the meetings of the Clinical Pathologists.

In my study of allergic sinusitis I have seen a number of cases of polyp formation. Whenever polypi were associated with allergy, the process was readily recognized histopathologically. I do not believe it is wise to state, and Drs. Kern and Schenck did not show in their histopathologic photographs, that every case of polyp formation is associated with allergy. Many instances of allergic sinusitis eventually form polyps but a routine examination of all sinus tissue will show just as many instances of polyp formation not associated with allergy.

DR. E. K. HANSEL, St. Louis.—The paper of Drs. Kern and Schenck brings out some very interesting points on the histopathology of allergy. Their observations are quite in agreement with those that we have made.

I believe there is some confusion as to the classification of nasal polyps. The polyp that occurs in allergy is an edematous polyp and is characterized by edema and eosinophilic infiltration. The term "mucous polyp" has also been applied to those which contain mucous glands. Allergic polyps may or may not contain mucous glands.

If we consider, first, the normal histology of the nose and sinuses, it offers an explanation of why polyps occur in certain locations. In the middle meatus, in the ethmoidal cells, and in all of the other sinuses, the mucous membrane contains a more delicate connective tissue stroma than that of the turbinates themselves. This stroma is almost of the myxomatous type as compared with the firm connective tissue of the turbinates.

The edema which occurs in the mucous membrane appears to be confined to the outer layer of the submucosa, where there is a thin strip of connective tissue between the glandular layer and the basement membrane. The edema seems to be confined almost entirely to this area, at least as far as the formation of polyps is concerned. A polyp represents simply the enormous stretching of this original small, narrow zone. This accounts for the fact that in most of these edematous polyps there is very little supporting stroma—the edema in the mucous membrane increases to the point where the stroma is unable to retain it so definite pedunculated polyps form.

Polyps do not form on the inferior turbinate. The edema occurs here, but I have never seen a pedunculated polyp in that location. On the lateral surface of the middle turbinate the mucous membrane has the characteristics of the ethmoidal mucosa, therefore, polyps may form at this site.

There are two types of nasal polyps in allergy cases, first, the nasal polyp which is the result of the edema of allergy, and second, the allergic polyp with secondary infection. Repeated acute and chronic infections produce an inflammation which increases the amount of connective tissue stroma in the polyp; sometimes to the extent of dense infiltration, with many lymphocytes and plasma cells. In other words there is the addition of an inflammatory process on the original allergic process. In those cases where polyps have been repeatedly removed, the recurring ones usually show an increased connective tissue infiltration.

There is another type of polyp which is primarily the result of suppuration. A long continued suppuration in the frontal sinus or in the antrum will produce, as a result of secondary irritation of the mucous membrane, the formation of an edematous type of polyp. In these cases there is no eosinophilic infiltration. There are, therefore, three types of edematous polyps: (1) the pure allergic polyp, (2) the allergic polyp with secondary inflammatory infiltration, and (3) the pure inflammatory polyp secondary to a primary suppurative process.

DR. SCHENCK.—I think the difficulty here is largely a matter of definition. We did not throw slides on to show a large series of polyps. It was merely to show what we meant by the type of polyp under dis-

cussion, the mucous polyp, or edematous polyp. It would take a half hour to define what we mean. When those definitions are ironed out, I think the clinical data will be rather conclusive.

I agree with Dr. Hansel's statements. I agree with his terminology. We do feel that this type of polyp which we are describing and which has been observed many times before (it is not a new thing) is the result of allergy. Because we do not always find the existence of the allergy is no reason for saying it is not of allergic origin, because in some of the cases we have presented we have had considerable difficulty in tracing the allergic part of the patients' story inasmuch as the patients were connected with other services, either the laryngologic service or the allergic service.

Adjuncts in the Treatment of Symptoms Frequently Associated with Allergy. SIEGFRIED MAURER, Chicago, Ill. (Abstract.)

This paper is a preliminary report on the use of urea nitrate, mucin pepsin mixture, and crystalline bile salts as adjuncts to the conventional treatment of allergic symptoms. Mucin has a secretagogue-like action and leads to production of mucin by the glands of the mucous membranes. Its use, therefore, in allergic cases where the mucous membranes are dry seems indicated. The administration of bile salts seems indicated in that they frequently alleviate itching. Urea nitrate is used in that it temporarily tends to decrease secretions from mucous membranes, and therefore is indicated where mucous secretions are excessive, and is contraindicated in cases with dry membranes.

These drugs have been used singly or combined on 70 patients with chronic urticaria, migraine, hyperesthetic rhinitis, gastrointestinal symptoms of allergic origin, hay fever, and asthma. The 70 patients so treated have received partial or no relief from conventional methods of environmental control and medication. When urea nitrate, mucin pepsin mixture, or bile salts, given singly or combined, were administered in addition to the treatment already received, the results were as follows: 30 per cent were completely relieved of symptoms, 50 per cent were partially relieved, and in 20 per cent there was no relief. In general, migraine, hyperesthetic rhinitis, chronic urticaria and gastrointestinal symptoms of allergy seemed to be most benefited.

DISCUSSION

DR. JOSEPH L. MILLER, Chicago.—I should like to know which one of these three things did the trick, the mucin and pepsin, the bile salts, or the urea nitrate. That is what we call in internal medicine a shotgun prescription. There must be some way of determining which of those things is really efficient without having to give all three of them.

DR. GEORGE PINESS, Los Angeles, Calif.—It has been my privilege to have some of this urea nitrate that Dr. Maurer speaks of. He sent us a large quantity of it, and we have tried it on the group of cases he describes.

The first case that it was used on was a case of serum sickness. About seven days following the injection of antitetanic serum this patient developed a typical serum sickness which continued over a period of several weeks, with an inability on the part of the attending physician to control the thing.

At the time Dr. Maurer sent me some of the urea nitrate, I thought this would be an ideal case to try it on. The dosage given was approximately six grains three times a day with food. This particular patient, who had no relief from adrenalin, calcium, and all the other therapeutic measures that were given, seemed to respond immediately. The itching stopped, the edema continued, but at the end of some thirty-six hours began to clear. Whether this was a coincidence, that it was time for the condition to clear up, or whether the urea nitrate was the factor that did it, I cannot say, but I believe that the itching's having disappeared as it did, the urea nitrate probably had something to do with this picture.

The next group that we studied was a group of urticarias, which everybody realizes are difficult to handle with anything at our command. Unfortunately, the urticarias in my experience have yielded the poorest results. The cases were individuals who were not studied from an allergic standpoint because of the acuteness of the symptoms, and in one individual because of the chronicity and the inability to do tests on her.

We did not use mucin or pepsin, or bile salts in any of these cases, but the urticaria patients got some measure of relief. In one particular case it seemed unusually quick, with permanent relief so far.

The interesting things about the use of the drug in these cases were the untoward symptoms the patients complained of. In one, particularly, it was a sharp pain in the abdomen immediately following the drug itself, which disappeared in half an hour. When the dose was cut down there was less pain, but the relief from symptoms was not so great.

Our success with the drug in the asthmatic individual was absolutely negative. We tried it in both types. We tried it in the so-called wet type, with a great deal of cough and production. It gave no relief so far as the cough and dyspnea were concerned. In the dry type it gave absolutely no relief. So those cases in which we got any measure of relief were the urticarias, and the one case of serum disease that I mentioned.

Dr. Harry L. Huber.—I received a supply of this medication from Dr. Maurer a short time ago and have had an opportunity to try it out on only a few cases.

We used urea nitrate on a group of patients diagnosed as nonspecific vasomotor rhinitis. About 20 per cent of them seemed to be helped for the first few days, but in most of them symptoms recurred, and when the medication was tried again there was little relief.

In three cases of chronic urticaria the symptoms were markedly increased each time they tried to use this urea nitrate.

I used some of the mucin pepsin and urea nitrate mixture on two cases of urticaria without beneficial results. The urea nitrate, mucin pepsin and bile salts combination was used in only one case where other things had failed to give any definite improvement and gave no

relief. I appreciate that conclusion as to the value of a medication cannot be drawn from such a limited trial in severe chronic cases that have resisted other types of treatment.

DR. GEORGE L. WALDBOTT.—I should like to ask Dr. Maurer what the rationale of his treatment is. Is there any evidence available in the literature which points to certain changes in the blood urea in allergic patients? What induces him to use urea as a therapeutic agent?

DR. A. H. W. CAULFEILD.—Dr. Miller said he gave a gunshot with three. I was under the impression that he used one or three. I should like to have Dr. Maurer tell whether he gave one or whether he gave three, as Dr. Miller interpreted.

DR. MAURER.—My method of using the urea nitrate, mucopepsin and bile salts cannot be termed a shotgun prescription. The patients first received urea nitrate. Those patients who were not benefited by the urea nitrate received mucin, and if not benefited by mucin, bile salts were tried. Several patients after receiving one at a time, received urea nitrate, mucin and bile salts at the same time. This series is too small to establish any one of these compounds as the most efficacious.

Dr. Huber and Dr. Piness have given their results with these compounds. Their experience with the urea nitrate indicates that it is of some value. The degree of value can only be determined by much larger series than so far exist.

In the dosage of urea nitrate we give 0.2 gram four times a day. It is safe to use. If it is beneficial, relief of symptoms will be at hand after a few doses have been taken. If marked relief is not obtained after the use of urea nitrate for three days, I usually discontinue it.

At present the uses of these compounds are experimental. If any one of them proves to be of sufficient value, the mechanism of their action will be worked out later.

The Antigen-Free Room in the Detection and Control of Cutaneous Anergy in Pollen Bronchial Asthma. I. S. KAHN AND EMMA M. GROTHAUS, San Antonio, Tex. (For original article, see page 45.)

Air Conditioning as a Means of Removing Pollen and Other Particulate Matter and of Relieving Pollinosis. WARREN T. VAUGHAN, Richmond, Va., and LAURENCE E. COOLEY, Dubuque, Iowa. (For original article, see page 37.)

DISCUSSION

DR. LEON UNGER.—I want to confine my few remarks to the first of these two papers, the one by Dr. Kahn on the allergen-free room in the detection and control of allergy in pollen disease.

I noticed Dr. Kahn used the words "allergen-free" room. He does not specify it as a pollen-free room. He specifies it as allergen free, leading me to believe the room has been kept clean of all allergens besides pollen. In other words, there are no feathers in the room, there is a minimum of dust, there is no cottonseed, and the mattresses are perhaps covered with rubber sheeting so that the room is really as free from allergen as possible.

I make that statement, first, because it brings into question some of his conclusions and results. Dr. Kahn states that he has only 76 per cent of positive skin tests in the pollen cases, and that the other 24 per cent are negative to intracutaneous tests, and negative to ophthalmic tests. In other words, 24 per cent of the cases are negative to intracutaneous and ophthalmic tests, and yet he considers them pollen cases.

He comes from San Antonio where the pollen is thrown out eleven months in the year, and we in Chicago have a pollen season of perhaps six months. Therefore, they have a much longer pollen season than we have. It seems to me that a human being is a human being whether in San Antonio, Chicago, Milwaukee, or wherever he is. I do not believe any other man doing allergy work has found similar results to this 24 per cent of negative pollen tests in cases which are considered truly pollen cases.

The thing that impresses me is the possibility that some of these 24 per cent of negative tests might not be pollen cases at all. They might be feather cases, they might be house dust cases, they might be sensitive to dog hair, cat hair, cottonseed, silk floss, or other things. The fact that he puts them in an allergen-free room and they get relief does not prove that they were originally pollen cases at all. They might be due to one of the other nonpollen allergens.

I should like to know whether these cases with the negative pollen tests were thoroughly tested for all the other proteins, for the dusts, feathers, cottonseed, weeds, orris root, and all the other things which we up North are so accustomed to test for routinely. I think a good many of us at least have adopted the idea of completely testing all our hay fever patients. For about five years we have tested all pollen cases with all the other proteins as well as the pollens. I think that is a very important thing, because to classify a pollen case as a pollen case, and yet have a negative intracutaneous and negative ophthalmic test is a very, very rare thing.

In our experience up North certainly not more than 0.1 per cent of our pollen cases will give us a negative scratch test, a negative intracutaneous test, and a negative ophthalmic test. We do all those in order. If we get a negative scratch test, we do an intracutaneous test, and if that is negative we do an ophthalmic test. If that is negative, the chances are we are not dealing with a pollen case. Of course, there is always the possibility of those patients being sensitive to some pollen not yet discovered, or not yet recognized, and therefore not tested for.

Dr. B. Z. Rappaport.—Speaking of the negative conjunctival tests, I want to mention that I recently have had several patients who had delayed conjunctival reactions occurring some twelve to twenty-four hours after the pollen had been placed in the conjunctival sac.

About this filtration work, after two or three years of quite intensive study that Dr. Welker, Dr. Nelson, and I have devoted to various types of filters (and I think we have seen all that have been put on the market, and have worked with several of them as well as with those specially designed), we wonder as to the usefulness of filters in asthma. I think the usefulness is quite limited, even diagnostically.

From a practical point of view, especially in the patient who gives a negative skin reaction, with the history not typical of seasonal asthma (and I presume in some cases it is rather difficult in Texas, even for an expert allergist to say he is sure that the condition is caused by pollen, when that patient is exposed to pollen eleven months in the year and is possibly sensitive to several different kinds of pollen), it seems to me it would be quite a problem to place a patient of that sort in filtered air.

Dr. Kahn, in a paper as early as 1926, spoke of several patients who required residence in the room for weeks, and one patient who required residence in the room for two months. Of course that period of observation is absolutely impossible from a diagnostic point of view.

If we were to depend only on the effect of confinement in filtered air for the diagnosis of the cause of asthma, I am sure there would be a number out of 100 or more patients we studied that we could not be sure were pollen cases, because of the slow and incomplete relief obtained in many cases. There is no definite time during which the symptoms will clear up, as Dr. Kahn pointed out.

As for the use of air conditioners, last year we used a Frigidaire conditioner probably of the type described here, and like that which Dr. Gay described in the *Journal of the American Medical Association*. Our work was conducted differently from the work that Dr. Vaughan did, in that we combined filtration and air conditioning. We had two wards, in one of which the air conditioner was placed and, in addition to the air conditioner, a pollen filter. That was a very efficient filter. Using the combination of the two rather than shutting the room up, we came to the conclusion that the room that was air conditioned was no better, as far as relieving symptoms was concerned, than the room in which the air was not conditioned. We were quite sure of that. In fact, we even had our doubts, on some days, whether the room was not much worse because of the cool air than the other room, although it was more comfortable to one who did not have asthma. But probably because of the increased humidity in that room we felt the asthma patients were at times distinctly worse. While our experiment and the one described here were not conducted under comparable conditions, we did not feel there was any great advantage in cooling the air, nor was the pollen count any lower in that room. In fact, it was the opposite; it was higher, which we believe was due to the less efficient filter than that in the other room.

Dr. Warren T. Vaughan.—I am interested in Dr. Rappaport's use of the combined filter and air conditioner. We did not use the filter because we wanted to know what would happen without the filter. The logical procedure, it seemed to us, was to use the conditioner alone. The conditioner certainly removes pollen, and the logical conclusion then would be that there was something the matter with the filter that let pollen get by. We used no precautions except to keep the doors and windows closed. We had a tremendous decrease in pollen count.

The next question with us was: Would it have happened anyhow in a room without a conditioner, with the doors and windows closed? For that reason we went ahead to see whether the conditioner would actually take pollen out of the air, which it did.

I rise principally to correct Dr. Rappaport on one statement. The humidity is always lower in an air-conditioned room, decidedly lower. The moisture is taken out of the air by the conditioner.

DR. ALBERT H. ROWE, Oakland.—I have a slide of an air conditioner that I would like to show. I have been using it for about five years at Peralta Hospital in Oakland.

(Slide) This conditioner was made in the hospital by the engineer, and is relatively inexpensive. It takes care of about four rooms very well. With its use we have been able to keep the relative humidity down to forty and fifty, and we have been able to filter the air by passing it through very efficient filters. The humidity is taken out of the room by blowing air with a very efficient blower up and down around refrigerating pipes in the cabinet which are connected with the refrigerating plant of the hospital.

There were two reasons why I installed this apparatus. I wanted patients in pollen-free rooms. I also wanted to study, if possible, the effect of low humidities on the symptoms of the asthmatic patient. It was my opinion, before I began to make these studies, that low humidity had some effect on the control of the asthmatic symptoms. That was largely due to the good results obtained by sending people from the Bay Region, down to Palm Springs, down to the desert, to Arizona or New Mexico, and I had an idea that possibly it was low humidity that was partly responsible for the relief these patients obtained. But I was not able to convince myself that low humidity in itself was very beneficial in controlling these symptoms.

Our lowest humidity occurs between August and the first of January. My food sensitive patients very often will go through the summer up to about September 15 very well, and many of them seem to gain tolerance to certain foods so that they are able to eat them without any difficulty. Then, about September 15 or October 1, their tolerance seems to break down in spite of the fact that the humidity is low. That seemed to coincide with the experience that Van Leeuwen reported recently in the *Münchener medizinische Wochenschrift*. He has made a study of asthmatic individuals who very definitely get worse around August 15 and September 1. After studying the meteorologic conditions, and the humidity, and the ionization of air in Holland and Germany in careful manner, he arrived at the conclusion that he could not tell why these patients get worse. I believe there is some condition in the atmosphere we are not aware of. I know this occurs around San Francisco, and that certain food sensitive individuals can tolerate foods in the summer, whereas they cannot about the middle of the fall, and I am quite sure it is not due to low humidity.

DR. TELL NELSON, Evanston, Ill.—I should like to put a slide or two on the screen.

In our work, Dr. Rappaport's, Dr. Welker's, and mine, we had a filter in with the conditioning unit. (Chart 1.) This is the temperature line, and this is the humidity line. This is the temperature line in the uncooled room, or the one in which there was no air conditioning unit. This was the temperature line in the room where we had an air conditioner plus the filtration. This was the humidity line in the room where we had only air filtration, and this one with the air filtra-

tion and the air conditioner. As you can well see, the humidity in the room with an air conditioner was a great deal higher than in the room in which we had only the air filtration, whereas the temperature ranged from 8 to 10 degrees lower during the entire season.

This may be reversed in a room where you do not pump in the air continuously from outdoors. That may be the gist of the whole matter. We are not here to say that you do not get it, but in the room where you have a filtration unit plus your air conditioner you will get a higher humidity. The Frigidaire people told us when we started

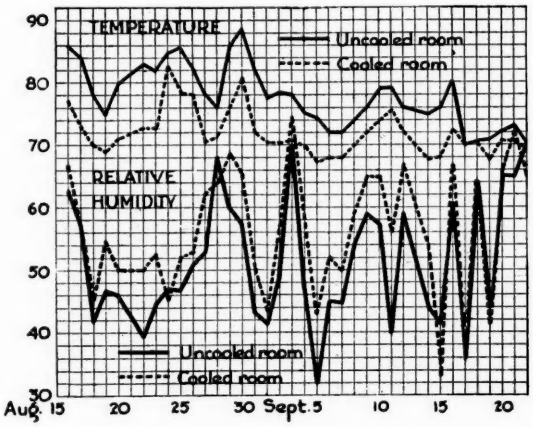

Chart 1.—Temperature and relative humidity in the uncooled and in the cooled wards.

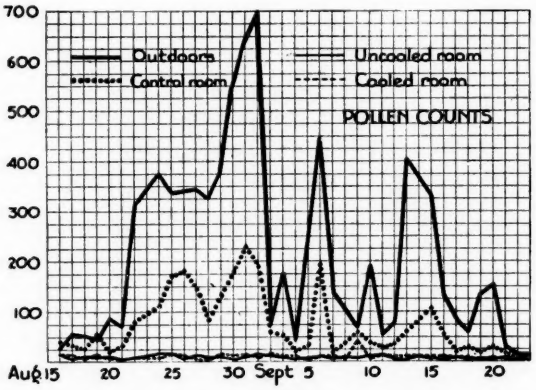

Chart 2.—Pollen counts outdoors, in the control ward and in the filtered air wards.

our experiment that the humidity would be lower, and they were very much surprised when we showed them our chart.

(Chart 2.) Here is the outdoor pollen count from last year in Chicago, and the count of the pollen in our control room. This heavy line is the pollen count in the room which was air filtered, and the checkered line is the one which had the air filtration plus the air conditioner. There was apparently no discrepancy except on one day, when we had a breakdown of our air filtration unit.

(Chart 3.) This shows the average time of onset of symptoms when patients go outdoors, which corresponds with the pollen peak; and the average time of onset of symptoms as compared to the average time of relief of symptoms.

I think the whole proposition of the humidity may be due to the fact that we pump air into our room continuously over the twenty-four-hour period, whereas in your particular instance, and in Dr. Gay's particular instance, there was no air pumped into the room. That may account for the difference in your findings and our findings.

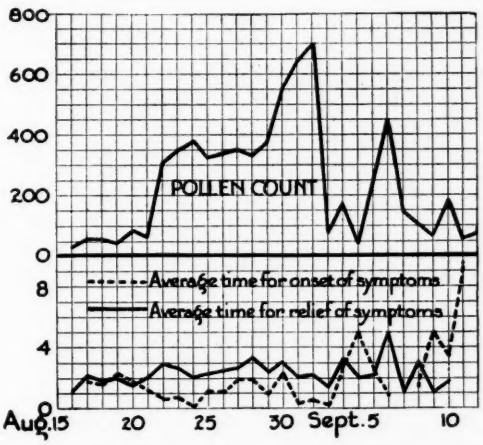

Chart 3.—Relationship of outdoor pollen count to the average time required for relief of hay fever symptoms in filtered air and for the onset of symptoms on exposure to pollen.

Dr. M. Murray Peshkin.—In discussing Dr. Kahn's paper I wish to state that even in New York City there exists a small group of patients (about 2 per cent) who have pollen intolerance with negative reactions to dry pollen in the conjunctival sac. There is no doubt that the figures in San Antonio are higher. Ten years ago only a few workers recognized the fact that a patient could suffer from a pollen syndrome and yet be negative to cutaneous tests. Today this clinical phenomenon is generally accepted to the extent that patients with pollen intolerance can even be negative by ophthalmic test to dry pollen. In this connection it is of interest to note that patients with positive histories of pollen intolerance who are refractory to pollen with any method of testing usually have asthma with or without hay fever. In other words, patients afflicted with only hay fever invariably show positive reactions to pollen by cutaneous test.

Specific pollen treatment in all of the foregoing groups of patients accounts for good results in approximately 70 per cent of the cases. What about the unimproved 30 per cent? For the latter group air filtration in conjunction with specific pollen therapy has materially reduced the percentage of failures. Aside from diagnostic purposes, the use of air filtration to the exclusion of hyposensitization treatment for pollinosis should only be advocated for the occasional patient in whom even the smallest dose of pollen causes an aggravation of symptoms. However, in the absence of economic or other reasons, such a patient will do better when removed to an environment free from the offending pollen.

The intelligent use of air filtration or reconditioned air in pollen asthma and hay fever should seriously concern all allergists. The type and number of apparatus are progressively increasing. The advertisements in the newspapers and magazines are written to appeal to the masses and accordingly cannot conform to the standards acceptable to the medical profession. Patients ask questions. They expect authoritative advice on these machines, especially with regard to their uses and limitations.

To begin with, the first practical pollen filter commercially obtainable for home use was introduced in this country in 1926 by Dr. Milton Cohen. In 1930, Dr. Beck and I described an improved filter which is obtainable in the market at one-half the price. In spite of the relatively low cost of these outfits and their ability to deliver from 200 to 450 cu. ft. of air per minute and also despite the fact that these apparatus were intended only as adjuvants to the hyposensitization treatment of pollinosis, the idea was not furthered by the allergist. However, the commercial sales value of treating hay fever with machines did appeal to the manufacturers with the result that the market is now flooded with all kinds of air filters and refrigeration units.

The use of reconditioned air for the relief of hay fever is not new. For years it has been known that hay fever was temporarily relieved in patients who remained in the type of refrigeration chest used in a large butcher plant. The present status of (refrigerated) reconditioned air as a means of relieving pollinosis is far from satisfactory. There are mechanical and economic problems to be surmounted before reconditioned air can be considered practical for use in the homes of hay fever patients. Reconditioned air is not filtered air and should not be confused with it. A patient who has become free from hay fever in an air-filtered room will, after leaving such a room, usually remain free from symptoms for varying periods of time. However, the same patient will have a recurrence of symptoms soon after leaving a room with reconditioned air. It is a common experience on a warm day during the pollen season for a patient with hay fever to spend some hours with a great deal of comfort in a modern moving picture theater. The patient is not relieved from symptoms immediately after entering the theater. More often at least one-half hour has passed before comfort sets in. After leaving the theater to strike the hot air outdoors, the symptoms of hay fever frequently and immediately return in an aggravated form. The patient with pollen asthma does not do well in cold atmospheres.

Some of the immediate objections to the use of refrigerated air in the home are (1) the absence of thermostatic control which permits of dangerously low temperatures during sleeping hours, (2) frequent chilling of the air beyond the point of comfort or else the pollen content of the air will be raised, (3) the bulkiness of the apparatus, (4) the air is unfiltered, and finally (5) the cost. A word need only be mentioned about the cost. The cost and installation of a refrigerated-air unit to service a small room ranges from $700 to $800. It must manufacture two tons of ice per day. The electric charges will easily be over twenty dollars per month.

In contrast to this, the cost of a reliable and practical air-filter unit, accepted by the Council on Physical Therapy of the American Medical Association, is about $75. The service charge is equivalent to that of

an ordinary electric bulb. No pollen will pass this filter when it is properly installed. On hot days the air in the room often becomes warm and stuffy, though bearable. This objection can easily be overcome by the installation of an additional machine.

In summation, a refrigerated-air apparatus to be of practical value in the treatment of hay fever must be thermostatically controlled to maintain humidity and temperature conducive to physical comfort, contain an efficient air-filtering unit and its purchase price and cost of maintenance be within reach of the average patient. The hope of fulfillment of all of these criteria in the near future is exceedingly dim.

In the final analysis, any type of acceptable apparatus modifying the pollen content of the air should only be employed in selected cases of hay fever as adjuvants to specific pollen treatment.

Dr. E. L. MacQuiddy, Omaha.—We have been battling this question of air filtration and air conditioning for the past three or four years, and the idea of expense has entered materially into it. I will give you a suggestion, and you can take it for what it is worth.

We have lately been using the glass wool filter as put out by one of the commercial houses, and testing it with the same means that has been mentioned here before. Using lycopodium as the pollen, we have found that two of the wool filters are efficient enough to keep out about 90 per cent of all the pollen. This type of filter has a distinct advantage in that it lets you draw through almost an unlimited amount of air without very much resistance.

In the Middle West we have the question of high temperatures and high humidities, so that in order to make the room livable at all we have to make an attempt at cooling. We have accomplished this by putting our unit in the basement. A good many of our homes are heated by hot-air furnaces. We simply connect our air filter in the basement to the hot air duct going to that room. By using the blower type (we have used the blower instead of the fan), and boosting it, we can get cooling by two sources: first, by air circulation which allows more evaporation from the body; second, by using basement air which is ordinarily about ten degrees cooler than the air in the second story where most of the people live.

We have not used this in a great many cases, but in those cases where we have used it we are certainly encouraged to continue its use.

Dr. Milton B. Cohen.—There are one or two things which I think men are in some disagreement about with respect to the field of usefulness of any type of air conditioner, which I believe ought to be cleared up.

No one would expect to keep patients permanently behind filters, or in air-conditioned atmospheres. You cannot put patients in glass houses. If we could, we would not have to do a lot of things we do in allergy. However, besides the usefulness that Dr. Peshkin has pointed out as an adjunct in handling your patient in whom you cannot get sufficient tolerance, these rooms do have a distinct place in the diagnosis when you are up against the problem of determining whether you are dealing with an extrinsic or an intrinsic case. It is true that occasionally a patient may remain a couple of weeks under controlled conditions and still the symptoms may not clear up.

In our experience, it has been of great assistance to pick the patient up bag and baggage and put him in a controlled situation to find out whether his symptoms will or will not clear up. We have had patients referred to us with the idea that they should have radical procedures done on their antrums or on their sinuses generally. Before we would allow such things to be done, we have said, "Before we can say this is an intrinsic case which requires perhaps such radical procedure, let us put this patient in a controlled environment." To our surprise, and the surprise of the clinicians sending them, very often they clear up, and demonstrate that the condition is intrinsic.

There is one thing I should like to know from Dr. Vaughan and Dr. Rappaport. Is there any way, in any of the commercial air conditioners at present on the market, to control the temperature of the coil? This is a very important thing because, after all, the cleansing efficiency of any kind of air conditioner depends upon the relative difference between the temperature of the coil and the temperature of the air for any given humidity, that is, relative humidity. The cleansing depends upon the fact that when you cool the air which contains a certain amount of moisture, you reach the dew point. When you reach the dew point, you get exactly what you get on a cold day in the wintertime. You get precipitation of the fluid material, water, together with any particles in it. The drops of water are usually formed around particulate matter.

If one wished to increase the cleansing efficiency of one of these air conditioners, it would be necessary, provided they were not at present sufficiently efficient, to reduce the temperature of the coils.

Theoretically, the patient ought to be more comfortable if you can reduce the temperature of the room. Practically, I believe if you have reduced the temperature of a room sufficiently by decreasing the temperature of the coil, in order to get really efficient filtration in one or two passages, such as Dr. Rappaport tried where he was bringing in outside air and recirculating the air through the conditioner, you would have to have a conditioner ten times the size. You have to pass the air many times over one of those coils before it is clean. If you get it efficient enough to clean the air, you will get the air so cold and will remove so much moisture that you will have to add reheating and rehumidifying elements in order to get the proper atmosphere.

Dr. A. M. Goltman, Memphis, Tenn.—My impression of conditioned air is that it means air which is relatively free from extraneous matter and at the same time is cooled to a temperature ten to fifteen degrees below that of the outside air, with a correspondingly lowered humidity. It has always been my opinion that the most important function of air-conditioning methods is proper filtration. Up until six months ago the method which I used for conditioning air seemed unsatisfactory because filtration was incomplete, and there was always leakage into the rooms in which the experiments were being made. At the present time, however, I feel that I have overcome most of the difficulties by using spun glass filters in series. In this way the air is passed through a series of six to eight filters before entering the room. At the same time the filtered air is forced into the room in such quantity that the air pressure within the room is slightly greater than the outside atmospheric pressure. This difference in atmospheric pressure has a distinct advantage in that it tends to keep extraneous material outside of the

room in case of faulty weather stripping or hidden leaks in doors, etc. Air is removed from the room by means of a suction fan. This suction, plus the increased atmospheric pressure, produces a double action in keeping the room allergen-free.

Conditioned air, or filtered air, is a valuable adjunct in the treatment of hay fever and asthma due to extrinsic causes for the following reasons: (1) It removes the cause of the disease, making the patient more comfortable and eventually relieving him in most instances while in the room. (2) In those cases in which treatment has been unsuccessful, while the patient is in a pollen- or dust-laden environment, conditioned air allows intensive treatment to be carried out, so that after a few weeks he may return to his former environment, and be relatively free from asthma. (3) In some of the cases in which no therapy has been successful, conditioned air often gives temporary relief. (4) In severe hay fever, conditioned air gives relief so long as the patient stays within the room, even though it is only for a few hours. This temporary relief is quite beneficial to the well-being of the patient.

I think that Dr. Kahn's attitude in regard to conditioned air is correct. Any adjunct in therapy which tends to give some measure of relief to a patient, is certainly worth while. My experience with conditioned air during the past six months has been most gratifying. It has a limited use, but in those cases in which it becomes necessary it is a most valuable aid.

DR. RAPPAPORT.—In the work that Dr. Vaughan did, I should like to know whether humidity readings were made. That is of considerable interest, because it is usually taken for granted that because the air is cooled the humidity will be lower. That is not the case, as Dr. Cohen brought out. The dew point may be reached by lowering the temperature ten degrees, which is all the patient will really bear. Still, while the humidity is lower, the relative humidity is not lower. So you have a room actually with a higher relative humidity compared to the temperature of that room, than the room that is not cooled.

I must take exception to Dr. Peshkin's remark about filters not passing pollen through. I believe I have examined most filters on the market, including the one he described, and the best I could say for any of them was that they were 97 or 98 per cent efficient, as compared with the air outdoors. The percentage of efficiency was not that high when we used a control room without any filter. If you compare it to such a control room without a filter, the percentage of efficiency is about 78 per cent.

All filters have this one common fault, that the air passes through them at very high speed. Parts of the filter become clogged, and the rest of the filter passes the air through at a much higher speed than you started out with. Pollen is passed through, and I do not know of any filter on the market (I think Dr. Feinberg will support me in that, because he was also the consultant on these filters) that is 100 per cent, or better than 78 per cent efficient compared to the pollen count in a control room.

DR. I. S. KAHN.—My paper was not on the details of pollen filtration or air conditioning. I have been using homemade and commercial filters for years, and by the frequent examination of pollen plates the

efficiency of filtration can be easily demonstrated. Such efficiency of filtration is easily securable to a high degree, and relief from their use in pollen cases is, of course, to be expected. I should merely like to emphasize the point that the continued use of pollen- and antigen-free rooms over a sufficient period of time will clear ultimately the vast majority of bronchial asthma patients no matter how old or how ill, provided the resolution of these cases is not interfered with by too early or too intensive testing, and that such rooms are almost indispensable to the allergy worker in heavy long-continued pollen environments, and that in the end results will show these negative skin test cases to be almost invariably of specific rather than infectious origin.

Why the number of negative skin test pollen cases in my community should be so high, I do not know. Colonel French of the Army Station Hospital in San Antonio secures a comparable percentage.

DR. LAURENCE E. COOLEY.—Regarding Dr. Peshkin's remarks about patients having symptoms immediately after getting out of the air-conditioned room, the one patient we had stayed in three days and after leaving the room was free for several days of her fever, even though the pollen concentration was very high at that time. About three days afterward she developed hay fever very severely again.

Of course, the cost of these conditioners is very high. It is only an adjunct. We do not attempt to use it in place of desensitization, but in occasional cases it is of value I believe.

Regarding Dr. Rappaport's question, the relative humidity during these experiments was 55 per cent. We spoke of one experiment where the humidity was raised to 96 or 98, but that was too high and moisture soon collected on the walls, and we had to stop the experiment at that time.

Regarding Dr. Cohen's question, the temperature of the coil can be regulated. The conditioner is best used during the summer months. Enough air will come in from the outside into the ordinary room to keep the humidity up. Of course, the conditioner does work much more efficiently when the humidity is up high enough so that moisture can collect on the coils. During the winter months, if the humidity drops down too low, the machine will automatically shut itself off. Therefore, it is not so efficient during the winter months.

The Preparation and Stability of Food Allergen Extracts. GORDON A. ALLES, GEORGE PINESS, AND HYMAN MILLER, Los Angeles, Calif. (For original article, see page 5.)

DISCUSSION

DR. M. MURRAY PESHKIN.—Dr. Piness has presented interesting and important information. The problem of maintaining the potency of fluid extracts of food substances has from time to time engaged the attention of all of us.

This morning I made the statement that a Coca extract of pollen (1:50 solution) will begin to show evidences of deterioration at the end of the second month, and for this reason pollen extracts older than two months should not be used. I have also observed glycerin ex-

tracts of pollen (equal parts of glycerin and Coca solution with 0.5 per cent phenol) kept under proper temperature conditions in medicine dropper glass bottles for diagnostic testing, show definite loss of potency at the end of six months. The P_H concentration of these solutions was not determined. Dr. Alexander recently reported that the large majority of allergists employ the Coca extract in the treatment of pollinosis. The presence of phenol, as Dr. Piness has pointed out, is largely responsible for the loss of potency in his glycerin food extracts, can easily be dispensed with since a 50 per cent glycerin extract remains sterile without any preservative. The exclusion of phenol or other preservative from extracting fluids containing no glycerin is not an easy matter.

It would not be remiss if the Society appointed a committee to determine the efficiency of all the common food materials in use. The present employment of all kinds of extracting fluids and methods of standardization has resulted in a veritable babel of languages so far as this phase of allergy is concerned. Would it not be better for all of us and for the subject of allergy if definite standards for test and treatment materials were adopted?

Dr. Leon Unger.—I should like to ask Dr. Piness how long his glycerin extracts retain other things than just the three he mentioned. How long do they retain their potency as a whole?

I ask that question because I have tried out some solutions made with glycerin, and at the end of about six months I noticed very marked diminution in positive reactions on scratch tests.

Dr. Albert H. Rowe, Oakland, Calif.—I will state at this time that in my paper on skin reactions to foods I am going to show that a good many of the intradermal commercial extracts of foods being sold to the medical profession today are unstable and do not give definite and satisfactory reactions in patients who are clinically sensitive to definite foods.

Dr. Piness.—I had intended to discuss the stability of pollen antigen in glycerol preparation. I think we are one of the first group to use glycerol in our pollen and food antigens. We now have preparations of pollen antigen that are more than ten years old, and we are preparing a similar study to this one. We hope to report a series of three studies, epidermals, pollens, and foods. We have a group more than ten years old at the present time, which are just as stable as they were when prepared.

Dr. Peshkin brings up the question of his solutions not being stable, and I think I can answer it in two very short words. The Coca solution is certainly not a bactericidal solution, nor is it as good a buffer solution as one can prepare. Besides, I think we tried to show that the tricresol or any of the phenol derivatives do not add to the efficacy or the stability of these preparations. I think if Dr. Peshkin will use the same glycerin solution, without the Coca solution, using instead merely plain buffer salt, his preparations will probably stay some time.

Dr. Unger questioned how long the glycerin solutions hold their potency with foods, pollens, etc. I believe they are stable and that their potency is not affected by their age, but I think keeping them

refrigerated may perhaps keep their peak higher than it would be otherwise. The potency is best proved by the tests as shown here, that it gives reactions in most cases with the older preparations.

The question of commercial preparations does not enter into this discussion, so far as I am concerned. I am not using them for comparison, nor am I particularly interested in them. But I do believe if the men will get together and use a stable solution, we probably will get more uniform results, as Dr. Peshkin said. I do not believe Dr. Peshkin, or any committee, can make all men use the same preparation and give the same kind of report.

Silk Sensitivity, With Especial Reference to Its Rôle in Atopic Eczema. KARL D. FIGLEY AND HOWARD J. PARKHURST, Toledo, Ohio. (For original article, see page 60.)

Neurodermatitis Due to Protein Sensitization. SAMUEL J. TAUB AND SAMUEL J. ZAKON, Chicago, Ill. (For original article, see page 53.)

DISCUSSION

DR. FRANK R. MENAGH, Detroit, Mich.—I was very much interested in both these papers, not because I have so much to contribute to them but because we have had in the past a good many of these patients. In fact, there have been a group of patients that have plagued us. They have been women. They have been allergic. They have had this typical dermatitis.

The difficulty, though, arose from the fact that nearly all of these women had other factors as well. Nearly all of them had endocrine problems, and the worst thing was they had all developed a psychoneurosis. With this psychoneurosis, of course, it was very difficult to do anything with them.

We did not do the careful studies that have been done here with regard to silk, but we did find that two of these patients reacted to silk. One of them, as soon as she wore silk, developed a very marked itching under the silk garment that was worn. The other one, however, as soon as she wore silk developed a generalized reaction, and it is that type of reaction I think that could probably be ascribed to inhalation.

DR. GEORGE PINESS.—These two interesting papers bring up several points that should be brought out at this time.

One is the vocabulary. I think if we will all use the same terms we will understand one another much better. My thought is, from what I have learned from both these papers, that these are both the same condition only they are called by different names, and I think instead of the two names it would be better to choose the one used by Dr. Figley of silk sensitivity. It might be called dermatitis, or it might be called anything you like, but I think we ought to get down to the same position we took at our Portland meeting regarding the vocabulary we would use in talking about pollen. We use technical terms, and we should get down to a sane vocabulary so we will understand what the other fellow is trying to discuss.

The method of testing these individuals brings out a rather interesting point, in that we are not in accord with the dermatologist. Since the dermatologists have come into the patch test, which seems to be such a simple thing, they have at every opportunity flaunted the

idea that the intradermal or scratch test is of no value at all in the so-called dermatitis of the skin. The fact of the matter is that the dermatologist, as a rule, is not in a position to do proper testing and therefore takes the line of least resistance and does the patch test, and claims positive reactions. After all, it is a matter of interpretation.

Dr. Figley and Dr. Taub bring out very forcibly the fact that skin reactions do occur by the orthodox method of testing, and I think we should advise the dermatologist that this does exist.

Another thing I should like to bring up is the frequency of silk reactions. That is not an uncommon reaction, and the reactions that occur from silk are taken very lightly and not considered a factor, as a rule. I felt that way about it myself, but in recent years I have given it greater consideration.

Another thing that should be considered in those who treat silk antigens is that the reactions which are severe require weak dilutions, and that the patients are clinically free very soon after treatment is commenced providing you do not attempt to push the dosage. If you push the dosage too fast and give it too concentrated, you get into trouble and many times have a difficult time getting out of it.

It has always been my practice, with patients I treat with silk antigen, that as soon as they are clinically free, despite the fact that they are skin positive, I stay on that particular dose and do not attempt to go any further. You will find your patient will soon get tired of coming to see you once a week over a period of a year or more during an attempt to desensitize him to the point where you get negative skin reactions. I think you will find reactions will be positive over a longer period of time than you or they anticipate.

The question of silk being an inhalant is brought out very forcibly in two cases I have seen. One was a child whose grandmother was in mourning and wore a big, black silk veil. Whenever that child came in contact with this grandmother, instead of developing a dermatitis the child would develop a bronchial asthma, which in my opinion is very good evidence that silk can be an inhalant.

Dr. J. Forman, Columbus, Ohio.—It seems to me one objection the dermatologist has had to skin testing has not been his inability to perform ordinary scratch and intradermal tests, but has been the fact that he has done it routinely for all forms of dermatitis, and so a very high percentage of his cases were not atopic individuals and therefore did not have the proper antibodies to show results. The result was he had a large number of negatives, and he decided therefore that the test was no good because he applied it to the wrong people.

There is another point I should like to make. I believe it makes a good deal of difference whether antigens used for the testing of silk are made from the silkworm or from crude silk. It seems to me with the silkworm you get altogether too many false positives.

Dr. Harry L. Huber.—Dr. Figley's demonstration that a local dermatitis may be caused by inhalation of an irritant clears up one question always raised by dermatologists. One of my patients who is sensitive to ephedrin had a severe generalized dermatitis following the ingestion of one 3/8 grain dose, and another has repeatedly had a local dermatitis about her right eye following a small dose of bar-

bituric acid. Are the patients so affected "nervously exhausted" as claimed by some of our dermatologists? These papers present evidence to prove that specific irritants may be of major importance in dermatitis.

DR. MILTON B. COHEN.—I think in relation to this problem of neurodermatitis and eczema that it is very important that we as allergists do not fall into the same mistakes that the dermatologists have fallen into. To most dermatologists dermatology is a specialty of nomenclature, and as long as they can hang a long name on the disease that is satisfactory.

We have fallen into the same mistake, because we have undoubtedly in the past, skin tested many patients of the type Dr. Figley and Dr. Taub have referred to as contact dermatitis. Epidermal sensitivity is what it really is. We have tested many patients by scratch or intradermal methods which demonstrate constitutional or dermal sensitivity. We have tested many by patch test, which demonstrates only epidermal sensitivity. When the dermatologist makes a patch test for dermal sensitivity, he gets no reaction and therefore he says, "There is nothing to this testing anyway."

I think it is extremely important that we differentiate these cases, and I believe in perhaps 90 per cent or perhaps a larger percentage of cases you can differentiate the two types as they walk into your office by ordinary clinical examination.

If you find a dermatitis or eczema, whatever you want to call it, any eruption of eczematous nature on the exposed surfaces of a body which occurs in an adult and which does not involve the folds, and which has vesicles (sometimes you do not find them in the chronic areas but at the edges), it is most certainly an epidermal sensitivity, and you will never get scratch and intradermal tests. If you have the type that does not have any vesicles, you do not need any patch test.

There is another point about the inhalation and ingestion of materials. If you see an epidermal sensitivity, so-called contact dermatitis, it does not make any difference how the active substance gets to that epidermis. If you have a patient who is sensitive to quinine, and the patient will give a patch test to quinine, the patient will also give skin lesions if he ingests quinine. The material may reach the epidermis via the blood stream or by contact.

Similarly, there is no reason to suppose that the inhalation of silk does not produce a lesion, such as Dr. Figley and Dr. Taub described. I have seen it a number of times, particularly since Dr. Figley called my attention to the likelihood of this being so.

One thing I should like to point out is that when you try to treat with silk you had better work very slowly. We exacerbated a girl with one to one million silk six months ago. We have been trying to get her well and give her some silk since then. We finally got her fairly well and gave her one part to one hundred thousand silk, which caused acute exacerbation. It seems impossible to give her any silk at all.

DR. B. Z. RAPPAPORT.—One of the things that Dr. Figley emphasized that has not been emphasized by those who have discussed this paper since, in spite of the fact that mention has been made of one to one million and one to one hundred thousand silk, is that here in this particular substance (and I think it is much more important than we have

heretofore recognized) there is a definite chemical entity, a definite protein substance we know something about which is the cause of the allergy.

In speaking of foods, we do not know what particular protein is the cause of allergy in food sensitiveness. We do not even know what particular protein is the cause of pollen sensitiveness; although some contributions have been made recently in New York that seem definitely to point to albumin as the probable cause.

In silk we have a substance which is composed of two main proteins, fibroin, which is insoluble, and sericin, which is partly soluble, and soluble to only a slight extent under ordinary circumstances. It depends upon what solvent you use in preparing the material as to what sort of concentration you will get. Sericin is soluble in about 0.5 per cent in distilled water. It is much more soluble if a slight amount of alkali is added. It is very soluble if it is heated. In preparing a silk solution it is immaterial whether you use the silk worm or the raw silk, you will get the same sericin, except that the silk worm has a lot of contamination from dirt. If you heat the material, you get a gelatinous preparation when it cools. The concentration of the antigen will depend upon the solvent used. Those who use an alkaline solvent get a much stronger antigen than those using ordinary saline or distilled water.

I think it is to be recommended that the dosage of silk should therefore be by nitrogen content, and you have the nitrogen determination of the protein if you use silk, not nonprotein nitrogen. I think silk sensitiveness is much more prevalent than mentioned by the authors. Some patients, however, are so mildly sensitive that it is difficult to diagnose the condition.

I had occasion to see one patient who had urticaria every Sunday. He happened to be very lightly sensitive to silk, and it was only when he sat in one particular chair, we discovered later on, that he got urticaria. That was a silk covered chair in which probably the sericin content was very high. He was negative to any sort of test, intradermal or scratch test, but he got a constitutional reaction to a subcutaneous injection of sericin in very weak dilution.

Used as wearing apparel, it is remarkable that silk is one of the most concentrated protein materials. Almost pure protein (sericin) comes in contact with the individual. No matter how much of it has been removed, at least 25 per cent of it is left in most of the silk fiber, so that pure protein is in contact with the individual.

Very frequently you will have patients who are silk sensitive who will tell you that the wearing of one garment only will cause symptoms. That is because that particular garment contains a lot more sericin than the other garments the patient has been accustomed to wearing.

There is one thing I should like to suggest to those who live in the East particularly, that there is a very fruitful field for research in silk sensitiveness. I took that subject up a few years ago and dropped it because there were no silk mills in this neighborhood. I was in communication with one of the largest producers, I think, in Philadelphia, and also with one in New York. They were very cooperative. They had several thousand employees in their mills at that time. These came in contact with much chryslis dust. These people frequently have skin lesions which are usually not attributed to the silk.

DR. C. MALONE STROUD, St. Louis, Mo.—Stokes and others have repeatedly emphasized the multiplicity of factors concerned in the production of eczema. Allergy is by no means responsible for the causation of all eczema.

I wish to refer briefly to one case which emphasizes the necessity of a complete study in the diagnosis and treatment of allergic patients. A carpenter, forty-nine years of age, came to our clinic suffering from a lesion of the skin confined to the elbows, popliteal spaces, buttocks and neck. The severity of the condition had been so marked as to incapacitate him for two years.

Intradermal skin tests revealed a four-plus reaction to wheat and a few inhalants. He was seen twice a week, and dietary restriction after the manner suggested by Rowe was employed. In two months he was only slightly improved. He was then seen by Dr. Eyermann who noted a definite increase in the size of wheals resulting from intradermal tests with cattle hair and several other inhalants. Dietary manipulation was employed along with various antipruritic medicaments. Slight but definite improvement resulted. In this clinic it was noted that he had an exacerbation on one occasion after contact with paint. He was sent back to Barnard Hospital for a period of time and entered the hospital where further improvement resulted, but the patient still had a large lesion on the buttocks and popliteal spaces. At this time the patient volunteered the opinion that turpentine caused an increase in his itching. His work had been of such a nature as to necessitate the handling of turpentine at intervals. A patch test of dilute turpentine oil was applied. Knowing that turpentine was irritating to anyone's skin, it was thought necessary to make a test on a normal person for comparison. Accordingly, a similar patch test was applied to my own skin. Within fifteen minutes the patient's patch test had to be removed on account of the severity of reaction. The patch test on my own skin was allowed to remain for an hour with no reaction. It was, therefore, concluded that the patient reacted abnormally to turpentine.

I wrote Dr. Coca about my findings in this case and asked for suggestions. He sent some syringes containing turpentine oil diluted with almond oil. The man was tested with almond oil, and it was found that he did not react to it. He was given injections of turpentine in almond oil. After the second injection his itching entirely ceased, and after the fourth injection his eruption entirely disappeared and he is now able to work. To date (October 9, 1933) he has not had a recurrence of his lesion. The last injection of turpentine in almond oil was given June 28, 1932.

The account of this patient emphasizes the importance of complete and thorough study, not only from an allergic point of view, but from a dermatologic point of view. We should use all means at our disposal in the interest of patients suffering from eczema.

DR. ALAN G. CAZORT, Little Rock, Ark.—About the importance of silk as an inhalant, I have in mind three cases, all having the typical distribution of the neurodermatitis. All three are multiple sensitization cases, two markedly sensitive to house dust, and having the worst symptoms when house dust asthmatics are worse. Another is very sensitive to Bermuda pollen with symptoms limited to the Bermuda grass season in my locality. Neither of the three is sensitive to silk.

I just wonder, if silk can be a cause or factor as an inhalant, why may not house dust, pollens, and so forth, be of equal importance?

DR. GEORGE L. WALDBOTT.—I wonder how the frequency of positive skin tests to silk compares with those of rayon and similar products. I have encountered reactions to artificial silk and rayon the number of which compares favorably with those obtained with regular silk.

DR. LEON UNGER, Chicago.—We have all enjoyed the papers of Dr. Figley and Dr. Taub. There is no doubt that they are both talking about the same thing.

It seems to me that the Society should choose one term for the conditions which they are describing. The term "neurodermatitis" is evidently a dermatologic expression describing the condition from the standpoint of the dermatologist. It does not convey much to the allergist, nor does it give us very much of an idea of the cause of the condition. I think we as allergists should stick to terminology which describes things from the allergic standpoint.

I therefore think we should all choose some term, such as "allergic dermatitis," in preference to "allergic eczema," eczema being a sort of wastebasket into which many different kinds of skin diseases are thrown. Allergic dermatitis should be used for those cases which Dr. Figley and Dr. Taub have described, which give positive scratch tests, positive intradermals, positive passive transfers, and which occur in atopic or allergic individuals; and which give negative contact tests. The term "contact dermatitis" should be restricted to the other main group which is due solely to contact with substances which, as pointed out, do not contain protein and which are evidenced mostly by vesiculation. If we use those two terms, "allergic dermatitis" and "contact dermatitis," we will have separated these cases very nicely, and will improve our results in treatment.

I should like to ask the two essayists about silk containing garments, because of the many varieties of material ranging from pure silk to silk-rayon combinations to rayon. How are we to prescribe for silk sensitive patients?

DR WARREN T. VAUGHAN.—Since we have gotten into a discussion of nomenclature, if you will pardon my getting a little away from the subject, there is a lot that should be done by a group of men who are talking allergy, in getting together on nomenclature and pronunciation.

On some of the simpler things we almost ought to form a committee! We have my′-graine, we have me′-graine, and we have megraine′. You find only one in the dictionary. You cannot find the others in it. We all say e-phed′-rin. You will not find it in the dictionary. It is eph′ed-rin. We talk about intradermal, a mixture of a Greek root and a Latin root. It is a bastard term that we should never use. We should say intracutaneous, or endermal.

DR. FIGLEY.—I realized when I brought up the subject of the term "eczema" I was rushing in where angels fear to tread, and I am very glad the discussion has not degenerated into an argument regarding nomenclature.

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You can see from the two papers that Dr. Taub and I are in complete agreement as to the clinical details regarding these cases. I do not care at all what terminology is used to describe this particular clinical entity. I only wish to emphasize that such an entity exists, that it is quite common, and that not infrequently silk sensitization is one of the factors in perpetuating this condition. I should be very happy if the term "allergic dermatitis" were settled upon for this condition so we would all be talking about the same thing.

I did not have an opportunity to read my case reports. In those case reports I discussed briefly some of the different silk materials that we tested with, and I wish to point out that it is rather important that one uses testing material which contains sericin. Some testing materials apparently contain so little of this that they are inert. In one case we missed the silk sensitivity for some time because of improper testing materials.

The material should be made from the raw silk, containing the gum. Recently I have obtained some material from one of the silk mills which goes by the name of "frison dust," which represents small particles of silk filaments which are too short to be thrown into a thread.

The point that was emphasized (Dr. Piness mentioned it, and some of the others) is that in these cases of atopic eczema, or allergic dermatitis, we are dealing with a constitutional sensitivity. Many of the dermatologists fail to appreciate that, and for that reason patch tests are of no avail. On the other hand, contact dermatitis represents simply an epidermal sensitivity, and in those cases the patch tests are the ones which give the positive findings.

Dr. Huber raised the point of the nervous exhaustion. I attempted to mention that in my paper in preferring the term "atopic eczema" to "neurodermatitis," because the term "neurodermatitis" does accentuate emotional and neurocirculatory instability factors, while in my opinion this condition represents a true immunologic problem with true constitutional hypersensitiveness as a basis.

In the patients I have seen, there is nervousness, neurocirculatory instability, and insomnia, and there are other features pointing to emotional and nervous instability. However, in my opinion, these factors are brought on by the intolerable itching. If the patients are nervous, it is largely because of this intolerable itching which is present day and night, and which prevents sleep. It is my belief that the nervous factor is not the underlying, basic, pathologic cause, but a secondary factor.

By the way, Dr. Pusey has emphasized that point very beautifully in his discussion of Rattner's paper—a paper entitled "Neurodermatitis or Contact Dermatitis," which was published in the December third issue of the *Journal of the American Medical Association* for 1932.

Dr. Rappaport brought up the question as to the solubility of silk, and I thank him for the information which he has recorded regarding that.

Recently, Goodman of New York brought out a monograph entitled "Silk Handlers' Disease of the Skin." In one particular silk mill Goodman was asked to study an outbreak of dermatitis affecting the silk workers. He found very definitely that this was a true contact dermatitis and had nothing to do with silk sensitivity whatsoever, but

was due to an antimildew substance mixed with neat's-foot oil. This antimildew substance contained a high percentage of creolin or creosol, which caused a purely phenol dermatitis.

There is one point I did not get to emphasize sufficiently which I think Dr. Cazort brought out, and that was in regard to house dust sensitization. Recently, at the Eastern meeting, Dr. Sulzberger emphasized this phase of neurodermatitis disseminatis, or allergic dermatitis, that many of these cases will require a dust-free environment before one can successfully clear them up.

I do not want you to go away with the impression that silk is the only inhalant substance to which these persons are sensitized. In three of the cases, house dust and bedding dust were a decided factor, and one woman cleared up entirely in a dust-free environment, which included removal of silk. Two of the patients were sensitized to mayfly, because in Toledo we have quite a bit of that, and two of them were very definitely pollen sensitized.

Just one other point, and that is in regard to what to wear in these cases of silk sensitivity. I have not found any of them sensitized to rayon. One can differentiate between silk and rayon microscopically. There is a distinct difference in the appearance of the threads under the microscope. So if you are in doubt as to whether the patient's wearing apparel is silk or rayon, the microscope will settle it.

DR. ZAKON.—From the discussion of these two papers, I am convinced more than ever that while allergists know allergy, they do not know dermatology, and while dermatologists know dermatology they do not as yet know allergy.

We have retained the term "neurodermatitis," not that we believe it is a good term, but because it has a definite place in the dermatologic literature, and because of the law in dermatology that a single agent may provoke many dermatoses and conversely numerous agents may produce the same picture. While silk may produce neurodermatitis, it may occasionally produce even vesicular dermatitis. Allergic dermatitis is only a group name, but is not specific, is not descriptive of the various dermatoses. Atopic eczema is not an ideal term, since neurodermatitis is not histologically an eczema. So I think instead of coining more terms, since we have sufficient already, we should retain the name as it is, as bad as it is.

What interests me most as a dermatologist is that the introduction of the allergic principle in the science of idiosyncratic dermatoses is a fundamental step forward. In the history of dermatology, in its development as a branch of internal medicine with cutaneous manifestations, there are definite periods each one contributing its share to the progress. Beginning with the gigantic task of Hebra of classifying the dermatoses according to their gross pathologic relations, then the period of histologic research culminating in the work of Kyrle, then the bacteriologic contributions added to the clarification of many an obscure condition, we have now arrived at the period of immunologic research which has already contributed many scientific observations and facts.

We must look at our present findings from a dynamic instead of a static viewpoint. It is possible that as our studies progress we may have to reinterpret our findings, but the factual findings will remain the same.

DR. TAUB.—I believe Dr. Figley answered all the questions that were discussed.

There is only one point. I think the various eczemas can be classified into three different groups: the occupational eczemas or contact dermatoses, the mycotic, and the allergic groups.

With reference to Dr. Unger's point of calling these allergic dermatoses, I think that is a very confusing term, because allergic dermatitis also includes the contact dermatitis as well as the atopic type of dermatitis. It is too general a term.

Studies in Pollen Potency. S. M. FEINBERG AND M. J. STEINBERG, Chicago, Ill. (For original article, see page 19.)

DISCUSSION

DR. WARREN T. VAUGHAN.—One particular question that Dr. Feinberg discussed can be very easily answered in a way corollary to the way he has made his study.

Does the extraction carry over all the potency or is some lost? If you will make an extract, a glycerol saline extract, or an extract in Coca's fluid, of a dried powder and extract it even as long as a week, and will then filter it and dry the residue and test the individual both with the extract and with the residue, you will get practically the same strength reaction from both, showing obviously that all the allergenic material has not been extracted.

DR. GEORGE PINESS.—In extracting pollen we have tried various methods. We find it makes no difference whether it is extracted for twelve hours or twelve months, we are not going to get any more out of the pollen grain by using buffered salt solutions, which is the usual extract. We find, too, that there is no change in freezing and thawing these solutions, in the amount of antigen we get from it. As I have experimented with antigens, I find it does not make much difference how you extract them, you are going to get that much extraction from them. Some time ago, Brown of Washington reported before this Society his ability to extract as much as 17.5 per cent, I think it was, of protein from his pollen grains. We have tried by this method and by other methods to extract that much, but we found it was impossible. The average extraction yields about 3 per cent.

As to the question whether or not these pollens retain their efficacy with age, I believe that any pollen that is well kept, that is properly preserved, and no moisture permitted to enter the bottle so that contamination and mold formation do not occur, will be just as active at the end of ten years as it is the first season it is picked. It brings up a point as to what changes might take place in pollens that are stored. Many who have collected large amounts of pollen have observed change in color of the pollen grains. That, in itself, is claimed by certain individuals who sell straight pollen, to decrease the efficacy and indicates deterioration of the pollen. I am not sure of that, because I can get reactions with that type of pollen just as well as I can with the other. The pollen that is moldy, desiccated in a desiccator or dried by running it through ether, does not yield a satisfactory pollen after you have finished, but given pollen, as I said before, that is put

into a sealed bottle and put in a dry atmosphere (we use a safe in which we have calcium chlorid tubes), we find we never have deterioration.

Where Dr. Feinberg shows reactions from year to year in his slides, I do not think is the measuring stick as to the activity of the pollen.

DR. ALBERT H. ROWE.—It might be interesting to some of you to know an attitude toward the preparation of bacterial vaccines which is being taken by Dr. Kruger in San Francisco at the University of California. This work was initiated by studies he made at the Rockefeller Institute, and it is the feeling of Dr. Kruger and a great many other men who have used these vaccines in northern California, that vaccine prepared by his new method produces better clinical results than do vaccines prepared by other methods. His vaccines are not killed by heat.

He puts them into a ball mill, and grinds them up so there are no evidences of the bacteria left. Then, for sterilization, he passes the solution through a colloid filter which he has developed.

I thought it might be interesting to try to prepare some pollen extracts by this method. I have used it with several pollens, and I have found that no better reactions have been obtained by the use of this method, grinding up the pollen granules so that there are no evidences of the grains left at all, and filtering them through these filters that he has recommended, than by the old standardized method I have used in the last few years.

DR. J. A. RUDOLPH.—I agree with Dr. Piness in his attitude toward the paper that was presented with regard to the concentration and age of pollen.

Three or four years ago we extracted pollen to make a 5 per cent solution. Following that extraction, we took the residue and reextracted the pollen. We treated two series of patients with these extracts and had equally good results with both. The subsequent year we treated two similar series of patients with the same extracts, a second extraction and primary extraction, and we obtained the same results.

There are no definite conclusions we can base on these observations. We have never published our results in these cases. I do not believe we can draw any conclusions with regard to age and concentration of these pollens at the present time. We have some pollens that are five and six years old, which are still as active as the day they were first prepared.

DR. B. Z. RAPPAPORT.—I do not see the mystery involved in the presence of activity in pollen after it has been extracted. It is due to the fact that all of the protein material is not extracted even on repeated extractions. Johnson and I, at the University of Illinois, extracted several pounds of ragweed pollen. I think Dr. Nelson followed it up with similar work. We extracted the pollen five times, and the fifth extraction showed activity proportional to the nitrogen content.

DR. M. MURRAY PESHKIN.—It appears from the authors' presentation that their pollen extract is at least double the potency of pure pollen grains as determined by comparative tests with the conjunctival method. These findings are extremely difficult of acceptance in the

light of the following data. Patients with a positive history of pollen intolerance exhibiting negative reactions to saturated solutions with the cutaneous (scratch and intradermal) and ophthalmic technics, will, in 98 per cent of the cases (in New York) show a positive reaction to the dry pollen grains by conjunctival test. It appears clinically evident that the saturated fluid extract of pollen is deprived of something which is retained in the natural dry pollen. A fluid extract of pollen is known to undergo some change besides a loss of potency as a result of Seitz or Berkefeld filtration. Finally, the ophthalmic test with fluid extract of pollen is not comparable to the dry pollen eye test, since the latter is Nature's test, for during the pollinating season the pollen causes symptoms by direct contact with the mucous membranes of the susceptible person, in spite of the fact that the patient be negative to the fluid extract of pollen with all methods of testing.

A word about intradermal testing to pollen solutions extracted with Coca and dextrose cresol solutions. Several hundred comparative tests have shown no superiority of the dextrose cresol extract over the Coca extract. It is not generally known that pollen extracts, with the exception of 50 per cent glycerin mixtures, begin to show a loss of potency after two months. The widespread practice of preparing pollen extracts other than the glycerin mixtures once or twice yearly should be discouraged for many obvious reasons.

DR. F. M. RACKEMANN.—As a measure of pollen potency, we have found that the scratch method, using serial dilutions of the extract, is by all means the best. We go by the last dilution which fails to give a positive reaction. We find that when we test by the intradermal method, we have to run the dilutions up to an extraordinarily high titer, whereas by the scratch method, which is not so delicate, the point where the test will fade out is reached much sooner.

So far as the skin test goes we think that this method of determining the potency of the extracts is sound. But a point I want to make, and I refer back to Dr. Caulfeild's paper read this morning, is that it is very important to understand the nature of the antigen involved. I, for one, am not convinced that the antigen which produces the skin test is the same as the antigen which is useful in the treatment of these patients.

DR. TELL NELSON, Evanston, Ill.—Dr. Rappaport mentioned a few minutes ago having extracted pollens five times. I carried the same procedure out and extracted the pollen fifteen times, using plain saline, drying the pollen in between and testing the patient to the dry residue.

Of course the skin reaction by scratch test depends on the sensitivity. We found our patients showed reaction to the tenth extraction, and we found that the dry residue, after the fourteenth extraction, gave a positive reaction.

QUESTION.—How large compared with the whole pollen?

DR. NELSON.—Very, very small compared with the whole pollen, but there was a definite reaction to the tenth extraction, and to the dry residue after the fourteenth extraction in some of our cases.

DR. GEORGE PINESS.—It appears to me that all this discussion brings out one point, that there is a definite saturation point, and that these things will only take up so much. It seems to me we are wasting a lot of pollen by not re-extracting, if what has been said is true.

The point I want to bring out is this: I cannot understand why whole pollen grains should give a greater reaction than a 1:50, or a 2 per cent solution would give if the saturation point is no greater than 2 per cent. How can they take up any more than that, except by irritation in the eye, with the pollen grain itself giving greater reaction? Dr. Peshkin says it does not give any greater reactions than the solution itself.

DR. PESHKIN.—No.

DR. A. H. W. CAULFEILD, Toronto, Ont.—Recently some rather interesting observations were made by a biochemist and botanist working in Toronto. If pollen is ground in distilled water and extracted in that way, practically all skin testing material comes out within about fifteen hours. The second extract is very weak, and the residue shows no reaction whatsoever on the great majority.

DR. RAPPAPORT.—That is in contradiction to the work Johnson and I did, in which the fifth extraction was with distilled water. We ground it in a ball mill.

DR. MILTON B. COHEN.—For purposes of the record, some one remarked a while ago that nonallergists reading the comments and discussions here this morning are going to be confused.

I happened to be present at the Kentucky State Medical Society when Dr. John B. Murphy was discussing a paper. Dr. Murphy had been criticized by some one for using a certain experimental type of treatment. In his discussion, he said he noticed in the discussion and the criticism that there was nothing said about any accurate observations as to the diagnosis or any particular amount of clinical information about the patient, but they just used Murphy's treatment. He then remarked that it did not make any difference, after you used good clinical horse sense, whether you used Murphy's treatment, so long as you used somebody's treatment with brains.

I wonder whether that is not one of the things that makes so much difficulty in our apparent disagreements about little points, whether to use this solution or that solution, or whether it be used intradermally or not. It seems to me when Dr. Phillips uses the intradermal method, and when Dr. Vaughan uses his subcutaneous method, and some one extracts pollen this way to get a solution, and some one else extracts it another way to get a solution, if they work intelligently they get results which are reasonably comparable.

To paraphrase Murphy, let's not just use the solution, but let's use it with brains.

DR. FEINBERG.—I am sorry that because of lack of time certain points in the paper could not be brought out which answer some of the points in the discussion. I also tried the scratch method. I tried to use all reasonable methods for comparison of these pollens.

I am certain that most of you, because of my hurried reading, missed the high point of the paper. It was not a comparison between pollen and pollen extracts. It is so well known that pollen extracts leave something behind after the pollens are extracted that I did not even think it necessary to mention it.

You remember I started with a hypothesis. This is a working hypothesis, or challenge, so to speak. Twenty pollen granules to which you are exposed naturally produce hay fever. Twenty thousand whole pollens, or the extract of this number, put directly in the nose do not produce hay fever. Why? I tried to answer that question in some of the experiments I tried. Unfortunately, I do not think I have answered them, but I still feel that if we can answer that question we shall have solved something very important.